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DEVELOPMENT OF BIODEGRADABLE IMPLANTS FOR USE IN MAXILLOFACIAL SURGERY

Annual/Final Report

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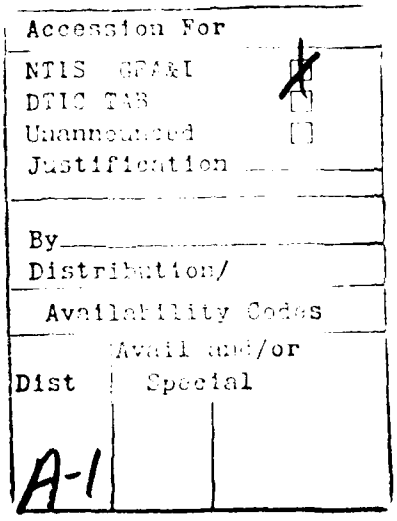

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19. ABSTRACT (Continue on reverse if necessary and identify by block number) Maxillofacial injury requiring open or closed reduction is a frequent result of modern military conflicts. Traditional reduction methodologies involve the use of metallic plates, screws, and wires, along with their associated problems. Therefore, biodegradable fixation appliances which should provide initial rigidity then gradually weaken so that newly forming bone is exercised have been investigated. Composite plates made from poly(DL-lactide) and reinforced with calcium metaphosphate (CMP) fibers provided the required strength but rapidly weakened when they were exposed to an aqueous environment because of a loss of polymer/fiber interfacial integrity. Methods to protect the fiber/polymer interface from fluid-attach techniques were investigated. Coating the plates with a hydrophobic, biodegradable polymer reduced the strength loss and smaller-diameter fibers and improved fiber wetting by the matrix, also resulted in more stable composites. Therefore, plates were prepared using these techniques for USAIDR's canine studies to repair broken mandibles. Replicate plates tested in vitro proved to maintain sufficient strength to provide the necessary support during the healing process.

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ABBREVIATIONS

poly(DL-lactide)	(DL-PLA)
poly(L-lactide)	(L-PLA)
polyglycolide	(PGA)
polylactide	(PLA)
ß-tricalcium phosphate	(ß-TCP), (ß-whitlockite)
phosplate-free calcium aluminate	(CaAl)
calcium metaphosphate	(CMP)
calcium hydroxyapitite	(CaHAp)
carboxylic acid	(COOH)
molecular weight	(MW)
polyacrylonitrile	(PAN)
US Army Institute of Dental Research	(USAIDR)
inherent viscosity	(IV)
flexural strength	(S)
flexural modulus	(E_B)
load at break	(P)
support span	(L)
width of beam	(b)
depth of beam	(d)
slope of tangent to initial straight line portion of load/deflection curve	(m)
American Standard Testing Methods	(ASTM)
molarity	(M)
three dimensional	(3D)
amorphous form of hydroxyapitite	(ACP)
hydroxyethyl cellulose	(HEC)
hydrochloric acid	(HCL)
scanning electron microscopy	(SEM)
poly(vinyl alcohol)	(PVA)
poly(ethylene oxide)	(PEO)
inch	(in.)
pounds per square inch	(psi)
volume by volume	(v/v)
hour	(h)
degrees Centigrade	(°C)
degrees Fahrenheit	(°F)
microns, 10^{-6} meter	(μm)
weight	(wt)
Polyacrylonitrile - Type A	(PAN-A)
dimothylsulfoxide	(DMSO)
parts per million	(ppm)
Angstroms	(Å)
milliliter	(mL)
milligram	(mg)
Lieutenant Colonel	(LTC.)
pascal	(Pa)

(continued)

ABBREVIATIONS (continued)

minute	(min)
millimeter	(mm)
that is	(i.e.)
phosphate buffered saline	(PBS)
polyhydroxybuterate	(PHB)
polyhydroxyvalverate	(PHV)
poly(hydroxybutyrate-co-valverate)	(PHBHV)

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I. SUMMARY

This is our Final Report on Projects 4150 and 5444, Contracts DAMD17-78-C-8059 and DAMD17-84-C-4039, "Development of Biodegradable Implants for Use in Maxillofacial Surgery". The objective of the project was to develop high-strength, high-stiffness, resorbable materials useful in the treatment of maxillofacial injuries. Our initial attempts to meet this objective were to prepare high-molecular-weight polymers and copolymers of DL-lactide (DL-PLA), L-lactide (L-PLA), and glycolide from high-purity monomers. These polymers were then used in the fabrication of polymeric bone fixation plates for evaluation of flexural properties and suitability as fixation appliances. Various model reinforcement schemes were also investigated using both nonbiodegradable, such as carbon and ceramic fiber and/or fabric, and biodegradable materials, ceramic and glass fiber.

Our initial attempts to fabricate plates for flexural testing were to injection-mold polymer samples. We found, however, that injection molding of the biodegradable polyesters required elaborate precautions to reduce moisture levels and heat exposure, which result in the rapid deterioration of the polymer's molecular weight (MW). Our alternative approach was the lamination of polymeric films to produce bone-fixation plates. A polymer solution was cast in a spin cup and the solvent allowed to evaporate. The resulting film was cut into sections, and the sections were laminated under heat and pressure to form plates suitable for flexural testing. No significant loss in molecular weight was observed for samples prepared by this method.

The lamination technique was easily adapted to allow for the addition of reinforcing fibers to the polymer films. Commercially available, nondegradable fibers, both ceramic and carbon, were laminated into biodegradable resins for use as a model system. In vitro experiments with these materials showed that the composites were capable of retaining sufficient strength and integrity in a pseudo-physiological environment, throughout the period normally required for formation of primary ossious union and subsequent healing. Implantation in dogs, conducted by the US Army Institute of Dental Research (USAIDR), demonstrated the patency of the fiber-reinforced resin systems in the promotion of healing in mandibular defects.

For the attainment of totally biodegradable fracture fixation systems, polyglycolide (PGA) reinforcing fibers were incorporated into the polylactide (PLA) resin. Fibers of PGA were melt-spun from high-molecular-weight polymer, and were knitted into a tube-shaped configuration and coated with PLA, but the resultant structure was too flexible for lamination. Commercially-available PGA sutures were then formed into a continuous web, the web was coated with polylactide, and the fiber-loaded film was laminated with other films of poly(DL-lactide) (DL-PLA). The flexural modulus of the resulting laminated sample, however, was judged to be too low.

To provide a biodegradable, reinforcing material with the sufficient strength and modulus biodegradable ceramic fibers were examined as reinforcement. Initially, we examined two bioabsorbable ceramic powders, ß-tricalcium phosphate (ß-TCP, whitlockite) and phosphate-free calcium aluminate (CaAl), as potential fiber-forming materials. Hard, dense ceramic test samples could not

be obtained from pure, packed powders of these materials. Therefore, alternative methods were examined to produce continuous ceramic filaments. Although dry spinning efforts were unsuccessful, wet-spinning mixtures of the materials with two different polymeric binders a terpolymer of acrylonitrile, butadiene, and methyl acrylate were found to be thermally stable. Ceramic loading, oxidative pretreatment, coupling agents, and sintering conditions were examined in an effort to improve spinnability and fiber properties. We were able to prepare only very weak fibers from both the calcium aluminate material and the ß-TCP. The fibers produced from these materials were, in general, highly porous and fragile.

Consequently, we examined bioabsorbable glass as a fiber forming material. Fibers of calcium metaphosphate (CMP), a totally bioabsorbable glass, were prepared by pulling from the melt at 1050 °C and air quenching. Smooth relatively uniform fibers were obtained by this procedure. The strength and stiffness of fibers prepared from this material approached those prepared from commercially produced glass. Initial composites fabricated by using DL-PLA as the binder and CMP fiber for reinforcement, exhibited strength and stiffness characteristics similar to those obtained with carbon or alumina-reinforced DL-PLA plates. After optimization of the processing parameters, we were able to draw long, smooth uniform CMP fibers using this process. Laminated composites fabricated using DL-PLA as the matrix material and CMP fibers for reinforcement exhibited strength and stiffness characteristics in excess of that reported for virgin bone.

The composites, however, exhibited a rapid loss of flexural properties both in vitro and in vivo, particularly when cut (such as occurs when drilling screw holes) or nicked. This phenomenon was thought to be the result of fluid wicking into the composite through the fiber ends, which ultimately destroyed the polymer/glass-fiber interface. Once this interface was destroyed, the composite rapidly lost its flexural properties. To alleviate this wicking, several methods were explored including; replacing the DL-PLA matrix with a more hydrophobic matrix, L-PLA; reducing the diameter of the glass fiber to more effectively coat the surface and provide better surface-surface interaction; and coating the composite with a more hydrophobic coating such as polycaprolactone, to reduce or resist the amount of fluid wicking into the composite. Although the wicking of fluid into the composite was not eliminated, we were able to make composite plates that retained a substantial portion of their flexural properties in vitro for over two months. Because the bone is thought to have healed sufficiently to sustain loading after approximately six weeks, we believe that this system should be adequate for repair of some mandibular fractures.

II. INTRODUCTION

The need for improved methods and materials for the management of severe maxillofacial wounds is well recognized in view of the substantial portion of these received by soldiers during conflict. It has been estimated that approximately 15% of survivable wounds sustained in modern military conflicts have involved the maxillofacial area. Of these facial fractures, about 40% required open or closed reduction. The majority of these injuries required

hospitalization, and ultimately resulted in prolonged or permanent loss from active military duty and subsequent loss of man-years of productive service.

Fracture fixation in maxillofacial surgery has traditionally been accomplished by the use of rigid metallic fixation plates or cribs with metal bone screws used to attach the appliance to the surrounding bone. This method of fixation is less than satisfactory for two reasons: 1) rigid fixation devices, which are of primary importance in the promotion of initial fracture union, may cause cortical bone to atrophy as the healing process progresses and 2) additional surgical procedures are required for removal after healing is complete, thus increasing surgical cost and patient inconvenience.

Ideally, fixation appliances should vary in stiffness as healing progresses, transferring an increasing proportion of the mastication forces to the mandibular bone as it becomes further ossified. This progressive load transfer ensures that the forming bone is strained and exercised. Both processes are necessary for the formation of healthy hard tissue that has properties commensurate with those of bone. The development of a variable-stiffness fixation device is best achieved by using a degradable polymer system with degradation products that are nontoxic and harmless to the host. A biodegradable material with properly tailored physical properties and degradation kinetics would ensure the development of strong, healthy bone and would eliminate the need for surgical removal of the fixation device on completion of the healing process.

Bone consists of a framework of collagenous fibers, a mineral matrix, which is primarily calcium hydroxylapatite, and a small amount of the polysaccharides. Even though a large portion of the volume of bone is water, bones are hard and tough. Although varying considerably in properties depending on function, bones commonly have tensile strengths of 6000 to 20,000 psi and values of modulus of elasticity of 1 to 3 X 10^6 psi. Metals are stronger and stiffer than bone. Most polymeric materials are as strong as bone but more deformable and require fiber reinforcement or crosslinking to equal the stiffness of bone. Because fibers of traditional resorbable ceramic materials such as tricalcium phosphate are not of sufficient strength for such a demanding application, CMP, a resorbable glass/ceramic, was evaluated to be the best fiber reinforcement for use in the polymeric plates.

Our evaluations have led to the development of a totally resorbable reinforcement plate, with retainment of sufficient flexural properties to provide adequate reinforcement to the bone. The successful development of this fixation system for the treatment of maxillomandibular fractures would obviate many of the predisposing conditions seen in the Vietnam era. Intermaxillary fixation either would not have to be used or would be used only briefly during the early phase of treatment. This would reduce the amount of man hours lost during convalescence prior to their return to duty, ultimately saving the Army both money and valuable service.

III. METHODS AND MATERIALS

A. Polymer Synthesis

Several approaches exist for the improvement of the mechanical properties of the thermoplastic polyesters. Both chemical and physical methods have proven useful for other polymer systems. In the numerous technical publications and patents which deal with improvement in the flexural and moduli strengths of thermoplastics, polymer molecular weight is the most common variable. Often, the flexural strength can be increased as much as ten fold by increasing the molecular weight of the polymer. For this reason, we prepared high-molecular-weight biodegradable homopolymers and copolymers from ultrapure monomers.

1. Monomer preparation

The first and perhaps most crucial step in any polymer development program directed toward improving properties is the preparation of high-purity monomers. This is especially true for biodegradable polymers of lactic and glycolic acids. Examples of our effort to obtain high-molecular-weight biodegradable polymers are given below.

a. DL-lactide

Crude lactide was added to isopropanol, and the mixture was heated at the boiling point until all the lactide dissolved. Heating was discontinued, and the mixture was allowed to cool slowly to room temperature. The mixture was cooled to 5 °C, and the crystallized lactide was isolated by inverted filtration. In the next recrystallization, one part of lactide was added to six parts of benzene, and activated charcoal was added. The mixture was heated to reflux and filtered while hot through a sintered glass funnel containing a bed of glass wool. The mixture was then heated to the boiling point again, and two parts benzene were removed by distillation to azeotrope out residual water. The solution was allowed to cool to room temperature. The crystalline lactide was isolated by filtration and protected from atmospheric moisture with a rubber dam during the filtration. The recrystallization from benzene was repeated twice more, without charcoal, and the lactide was dried under vacuum and heat. The monomer had a melting point of 126-127.5 °C.

b. L-lactide

L-lactide was dried in vacuo at room temperature for 24 hours. The crystals were then transferred to a round-bottom flask, and ethyl acetate was added in the ratio of 1 mL of ethyl acetate per 2 grams of lactide. The mixture was then brought to reflux for several hours until all the lactide was dissolved and the solution was allowed to cool overnight. Crystallization was enhanced by packing the flask in ice for several hours. The crystals were then collected, and the recrystallization procedure was repeated a minimum of three more times. At the end of the last recrystallization cycle, the crystals were collected and dried in vacuo for 24 hours.

All handling of the L-lactide crystals was conducted in a nitrogen-filled glove box under nitrogen purge. All glassware was oven dried at 150 °C for 24 hours, and assembly was carried out inside the dry box.

c. Glycolide

Glycolide monomer was prepared and purified by the following method. 65% aqueous solution of glycolic acid was placed in a three-neck flask equipped with a thermometer, a distillation head, and a condenser. The mixture was heated to boiling, and the water was distilled off. When the water ceased to distill, the system was placed under a water-aspirator vacuum, and the mixture was maintained below 180 °C until the reaction water was completely removed. The resulting molten low-molecular-weight PGA was slowly poured into stirred isopropanol at 5 °C, and the prilled material was collected as a light brown solid on a Buchner funnel. The polymer was dried in a vacuum oven at room temperature for 24 hours.

The low-molecular-weight PGA was separated into smaller portions and thermally cracked to form glycolide. Glycolide was catalyzed in a three-neck flask, connected to two additional flasks utilized as receivers for the glycolide, with 1% antimony (III) oxide. The pressure of the system was reduced to about 3 mm, and the temperature was raised to about 270 °C over 8 hours. The crude glycolide distilled as it formed and was collected as a solid in the traps, which were cooled with dry ice and acetone. The light yellow distillate was melted and poured slowly into isopropanol at 5 °C, and the prilled glycolide was collected by filtration and protected from atmospheric moisture with a rubber dam during isolation. The yield of glycolide was 920 g (92%).

Several portions of prilled glycolide were combined and recrystallized twice from dry ethyl acetate. The purified monomer was dried in vacuo in a desiccator heated to 60 °C. The melting point of the purified glycolide was 79-80.5 °C.

2. Polymer preparation

One approach to achieving a high-molecular-weight polymer from cyclic monomers was the use of a chain initiator in the polymerization to start the growth of just a few polymer chains. The resulting polymers generally are comprised of relatively long chains, and the number of chains approximately corresponds to the number of molecules of initiator. Lauryl alcohol was commonly used as the chain initiator in the preparation of various molecular weight polymers of DL-PLA and L-PLA. Typical syntheses for these polymers and for polyglycolide, using antimony trifluoride as a catalyst, are described in the following sections.

a. DL-PLA

The following procedure is representative of that used in the preparation of a typical batch of DL-PLA. In a dry, 2000-mL, three-neck flask equipped with a mechanical stirrer and a nitrogen inlet was placed 1500 g of DL-lactide, 15 drops of lauryl alcohol, and 0.3 g (0.02%) of tetraphenyltin. The loading of the reaction vessel was carried out in a nitrogen-filled glove box. The flask was removed from the dry box, connected to a nitrogen line, and placed in an oil bath preheated to 170 °C and stirred for 3 hours. Stirring

was then discontinued, and heating was continued for an additional 18 hours. The polymer was allowed to cool to room temperature, and then it was frozen in a dry-ice bath. The flask was broken, and the frozen polymer was removed and dissolved in methylene chloride. The viscous solution was poured slowly into stirred methanol, and the precipitated polymer was collected and dried in vacuo at 50 °C.

Attempts to increase the molecular weight of the polymer by varying the amount of lauryl alcohol were unsuccessful. A limiting step was reached whereby the addition of additional lauryl alcohol had no effect on the molecular weight of the polymer. Further attempts to increase the molecular weight of the polymer by this method were abandoned.

b. L-PLA

L-PLA was also prepared in our laboratories by a procedure similar to that used for polymerizing DL-lactide. L-lactide, freshly recrystallized from benzene, was dried in vacuo for 24 hours. Oven-dried (150 °C, 24 hours) glassware was assembled in an atmosphere of nitrogen. Tetraphenyltin (0.029%) and lauryl alcohol (1 drop from a standard Pasteur pipette) were added to 100 grams of the heated lactide. Heating was then continued at 170 °C for 18 hours, and stirring was continued until the polymer became too viscous to stir, usually four to six hours. During the polymerization process, the contents of the reactor vessel were kept under a nitrogen (ultrapure) atmosphere. After the polymer was cooled, it was dissolved in dichloromethane and reprecipitated into methanol to remove traces of monomer and low-molecular-weight fractions. After it was dried overnight in vacuo to remove the methanol, the inherent viscosity (IV) of the polymer was determined in chloroform. The inherent viscosity is used as an indication of MW, the higher the viscosity, the higher the MW. For the upper limit, typical values of 1.5-2.0 dL/g were obtained.

c. PGA

Purified glycolide monomer was placed in a flask and distilled into a flask for polymerization. The polymerization flask was equipped with a mechanical stirrer and a gas adapter. Antimony trifluoride, 0.03% by weight, was added as a catalyst. The reaction vessel was connected to a nitrogen line and placed in an oil bath at 170 °C. Stirring was begun when all the glycolide had melted. The reaction was stirred for 2 hours and 40 minutes at which time it became too viscous to stir. Heating was continued for another 6 hours and then the polymer was allowed to cool slowly for 16 hours. The reaction flask was broken away, and the polymer was ground in a Wiley Mill. The ground polymer was demonomerized by heating it at 130 °C under vacuum for 132 hours. The inherent viscosity of the resulting polymer as measured in hexafluoroacetone sesquihydrate at 30 °C was 1.27 dL/g.

3. Copolymer synthesis

One method of controlling the biodegradation rate of the bone-plate materials was to use copolymers of lactide and glycolide. The copolymers with higher glycolide content tend to degrade faster in vivo. These copolymers also exhibit distinct advantages in physical properties, particularly higher values of modulus, a result of the higher degree of crystallinity of the

glycolide. For this reason, we investigated the synthesis of block copolymers of lactic and glycolic acids.

Because higher MW PLA was available and because low molecular weight PLA is needed in the synthesis of PLA copolymers, we initially prepared low molecular weight PLA by steam autoclaving higher MW polymer. Figure 1 depicts the correlation between inherent viscosity and autoclave-time for a 1 g sample autoclaved at 120 °C and 15 psig. From this plot, we selected the appropriate time to autoclave larger amounts of PLA. This polymer was then used in the attempted synthesis of several block copolymers. However, high molecular weight copolymers could not be produced from this polymer, and other copolymers had to be synthesized.

The difficulty in producing high molecular weight copolymers of glycolide and lactide rests in the difficulty in obtaining pure glycolide and in the catalyst selected. To test the glycolide purity as well as the polymerization conditions, approximately 100 g of 75/25 DL-PLA/PGA were prepared. The same catalyst and reaction conditions were employed as were used in the preparation of DL-PLA described previously. The copolymer thus prepared had an inherent viscosity value, although it was less than that obtained for the DL-PLA homopolymer, still representative of a high-molecular-weight material.

Because of the slight decrease in viscosity with the 75/25 copolymer, a different catalyst was used to prepare 50/50 copolymer of DL-lactide and glycolide. Rather than the tetraphenyltin and lauryl alcohol catalyst and initiator system used for polymerization of DL-lactide, we used antimony trifluoride as the catalyst without the addition of a chain initiator. Antimony trifluoride is commonly employed as the catalyst for glycolide polymerizations. The 50/50 copolymer obtained from this polymerization had an inherent viscosity of 1.02 dL/g measured at 30 °C in hexafluoroisopropanol. PGA solvents such as hexafluoroisopropanol were required to obtain the proper chain extension in solution. The viscosity value of this copolymer represented high-molecular-weight material suitable for lamination studies.

4. Polymer fractionation

Because the biodegradable polyesters are polydisperse materials with wide molecular-weight ranges, the polymers contain high-molecular-weight material mixed with a significant portion of low-molecular-weight oligomers. Separation of the high-molecular-weight portion from the oligomers should give polymers with higher molecular weights than normally obtained in polymerization. A technique for the fractional precipitation of PLA was developed and employed to fractionate PLA with an initial inherent viscosity of 1.33 dL/g. The results obtained are given in Table I.

Because no significant increase was obtained, the polymer with an inherent viscosity of 1.60 dL/g was the highest-molecular-weight PLA that we obtained, we abandoned this method.

All the polymers that we prepared for fabrication into test samples were characterized by inherent viscosity measurements and differential-scanning calorimetry. We also developed a procedure for determining the number of carboxylic acid endgroups in PLA to determine the percent reactivity as an indication of molecular weight. Essentially, the procedure consisted of

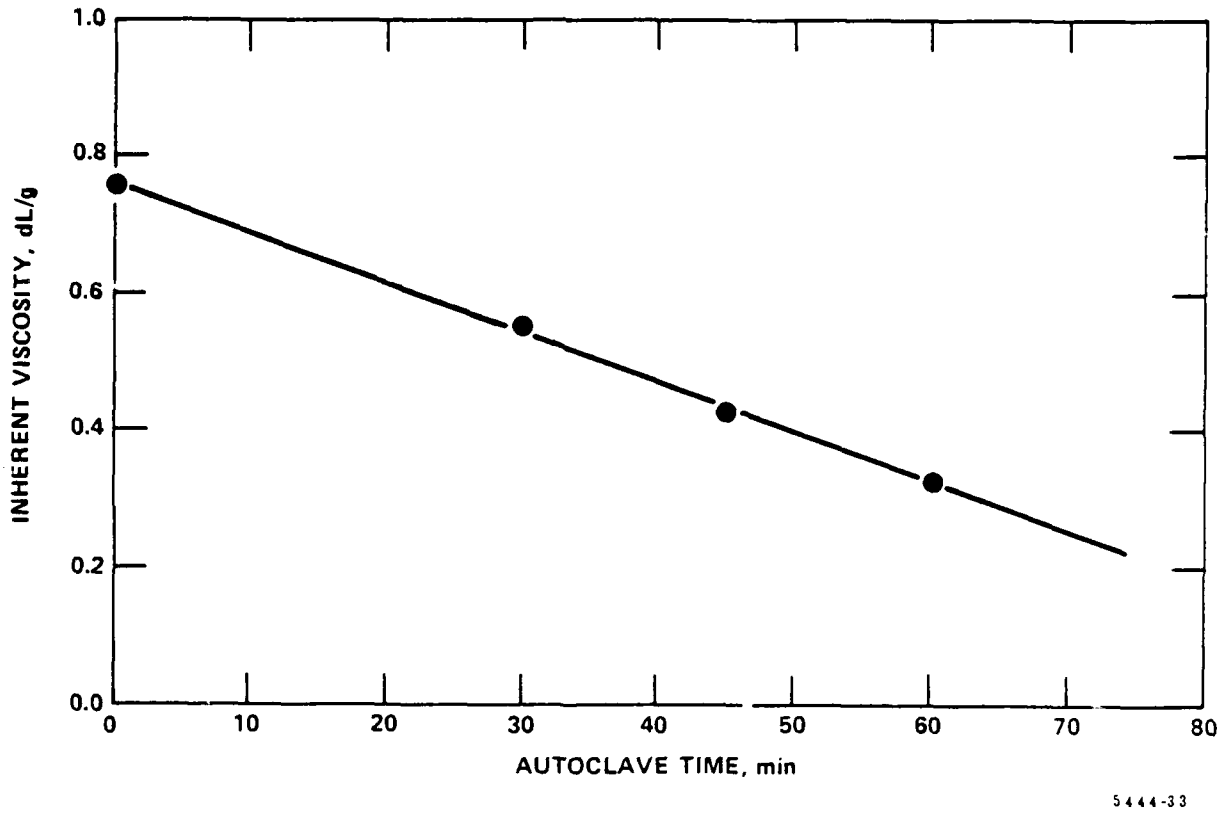


Figure 1. Inherent viscosity of PLA as a function of time in autoclave.

TABLE I. FRACTIONATION OF POLYLACTIDE

Polymer Fraction	IPA Added. mL	Polymer Wt. g	Polymer Recovery	Inherent Viscosity, dL/g
1	1300	44.27	63.2	1.60
2	165	10.24	14.6	1.16
3	140	--	--	--

dissolving the polymer in chloroform and titrating to a phenol red endpoint with 0.1 N sodium hydroxide in benzyl alcohol. As expected, initial results indicated that the number of titratable endgroups varied inversely with the polymer molecular weight (inherent viscosity). As Figure 2 indicates, a linear relationship existed between the inherent viscosity and the number of carboxylic acid (COOH) endgroups (equivalent COOH/10^6 gm). In addition, we found that as much as 0.5% of lactic acid (or its equivalent) was removed from the polymer when it was precipitated from dioxane into water.

B. Fabrication and Testing of Prototype Fixation Plate

To determine the physical properties of prototype fixation plates, we initially prepared plates from biodegradable polymers and copolymers. Attempts to injection mold and laminate these plates yielded samples with insufficient strength and modulus to be used as bone-plate fixation appliances. Attempts to increase the strength of these plates mechanically also failed. Because commercial materials reinforced with glass and carbon fibers proved to have superior properties to unreinforced material, we then attempted to increase the strength of our biodegradable polymers with fibrous reinforcement. Nonbiodegradable fiber-reinforced polymer showed such an improvement in plate strength that we then attempted to locate a degradable reinforcing material. Although we were unsuccessful in locating a ceramic reinforcing material, we did obtain sufficient strength with a biodegradable glass fiber, calcium metaphosphate (CMP). The physical properties of these plates were then refined to achieve an appliance suitable for use in bone-fixation.

1. Preparation of polymeric test specimens

The DL-PLA polymer prepared described previously was then fabricated into samples 3 in. X 0.5 X 0.125 in. for flexural testing by an ASTM method. In the initial fabrications, we used melt-injection equipment, but we later changed to lamination of cast films due to polymer degradation during injection-molding.

a. Injection molding

Two predried samples of DL-PLA (IVs = 0.45 and 1.30 dL/g) were injection molded at 135 °C and 225 °C, respectively. Upon visual examination of the molded samples, the higher MW DL-PLA had apparently degraded. Inherent viscosity measurements of the molded polymer confirmed this observation (a decrease in the IV from 1.30 dL/g to 0.7 dL/g). This was a result of prolonged exposure to heat, moisture, and oxygen, which rapidly degraded the DL-PLA. Because exposure to air during the molding process could not be eliminated, an alternative method was investigated.

b. Lamination

As an alternate method of fabricating samples, lamination of polymer films was investigated. Thin films of DL-PLA (IV = 1.25 dL/g) were prepared by a spin-casting technique. A dilute solution of the polymer in 1,1,1-trichloroethane was added to a teflon-coated cup which was rotating at 3500 rpm. To remove residual solvent, the films were dried in vacuo. The films

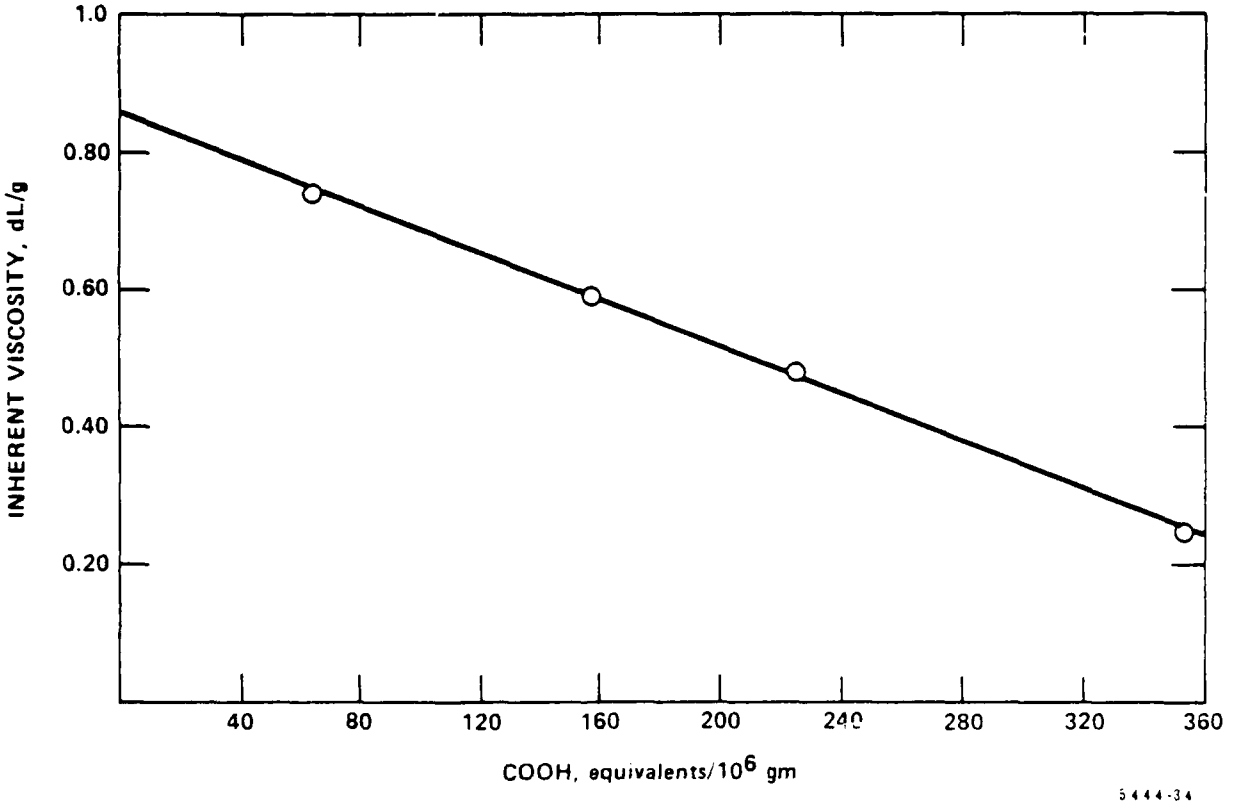


Figure 2. Plot of the equivalents of carboxy endgroups versus the inherent viscosity of DL-PLA

lamination. The laminate appeared to be a homogeneous structure when viewed in cross section. Similar films were prepared with dioxane as the casting solvent. This method of sample preparation resulted in a small inherent viscosity loss (approximately 5% of the initial viscosity as compared to approximately 50% of the initial viscosity of the injection molded polymer).

c. Annealing

To improve the flexural strength of injection-molded PLA samples, the effect of annealing on their mechanical properties was studied. Annealing plastics have often yielded high-strength materials by elimination of indicated stresses. The temperature and duration of the annealing process is usually dictated by the glass transition temperature and thermal stability of the specific polymer. If residual stresses were incorporated into the sample as it cooled after the molding process, annealing the sample should have removed these stresses and increased the material's resistance to fracture. Annealing a sample for several hours at a temperature close to the glass--transition temperature allowed the polymer segments to realign themselves in an orderly fashion. However, the resulting sample did not have improved physical properties. Apparently, the injection-molded samples of amorphous PLA did not benefit from annealing.

d. Orientation

As a unique approach to increasing the strength of the polymeric plates, we examined the method used by suture manufacturers for increasing the strength of polymeric fibers. In the production of synthetic sutures, the melt-spun fibers are rarely strong enough to be useful when they are first spun. However, if the fibers are drawn in the presence of heat, the mechanical properties increase dramatically. The drawing process aligns the polymer chains and affords a high degree of orientation. Almost all synthetic fibers are treated in a similar fashion, but the process is not as widely used for other plastics of different geometry.

Therefore, we chose to evaluate the effects of this process on a laminated sample of DL-PLA. A sample, 1 by 0.25 by 3 in., was prepared and oriented by drawing it to two times its original length at the rate of 2 inches per minute in an Instron equipped with a heating chamber. Although problems were encountered with the sample "necking" and slipping out of the clamps, a sample was obtained suitable for testing. These results are reported in Sections 3 and 4.

2. Preparation of fiber-reinforced polymeric test specimens

Incorporation of reinforcing fibers in polymeric materials has proven to be a useful procedure for improving their mechanical strength. Short fibers of glass, carbon, and synthetic polymers have been incorporated within polymer matrices as inert fillers, and woven fabrics have been impregnated and laminated with plastic and elastomeric films. These approaches offer advantages in improvement of mechanical strength and stiffness.

a. Nonresorbable fiber reinforcement

One method of reinforcement was the use of nonresorbable fiber such as carbon and ceramic fibers. Carbon fibers had been shown to be bicompatible, posing no threat to the body if they were unable to migrate from the implantation site. Other investigations had shown that carbon fibers were encapsulated by the regenerating bone as healing proceeds. Because high-modulus carbon fibers are well known for their ability to improve mechanical properties, such as flexural strength and modulus in other composite materials, we investigated their ability to improve the properties of biodegradable polymer. As an alternative approach, we also examined ceramic fibers. Due to advances in the ceramic industry, relatively inexpensive ceramic fibers had become commerically available and were becoming more prevalent in industrial products. Several of these fibers such as Nextel, appeared suitable for use in biomedical devices. For these reasons, and because of their superior properties, we elected to examine ceramics fibers as possible reinforcing materials.

1. Preparation of films

We prepared DL-PLA films reinforced with both fabrics and yarns to determine the utility of the materials in the fabrication of fracture-fixation plates with improved flexural properties. We used fabrics of both carbon and ceramic fibers. The carbon fabric was produced by carbonization of a fabric of rayon yarns. The ceramic fabric contained 3M Company's Nextel 312 ceramic fibers. Non-reinforced PLA films were used to fabricate control samples.

Films of PLA were prepared from polymers having inherent viscosities of 0.58, 1.14, 1.27, and 1.33 dL/g as measured in chloroform at 30 °C. These viscosity values represent low- and medium- molecular-weight polymers. All of the PLA films were prepared by the method described previously. P-dioxane was used as the solvent. A similar procedure was used for the preparation of fabric-reinforced films. The p-dioxane/PLA solution was injected into Mylar-lined spin cups. When most of the solvent had evaporated, a sheet of the carbon or ceramic fabric cut to the same 3 x 9 in.-size was placed in the cup onto the tacky PLA film. Additional PLA/p-dioxane solution was injected into the rotating cup, and the solvent completely evaporated. The dried film was then cut into 3 x 0.5 in. strips.

The preparation of the fiber-reinforced films required a different procedure from that used from the PLA and fabric-reinforced films. Fiber was slowly wound around the outer surface of a 4.5 in. diameter plastic jar. A solution of PLA in p-dioxane was sprayed on the band of yarns. Subsequent coats of PLA were applied and dried until the exposed side of the fibers was completely covered with polymer. The thin film containing fibers and polymer was removed, dried, and the uncoated side of the fibers was then coated with PLA until the fibers were completely enclosed in a polymer matrix. The fibrous film was dried and cut as described previously. We used both carbon and ceramic fibers. The carbon fibers were Thornel 300 graphite yarns, produced by Union Carbide from a pitch precursor, and Thornel 50 carbon yarns, produced by carbonization of polyacrylonitrile (PAN). The ceramic fibers were Nextel AB 312 obtained from 3M Company and Fiber FP developed by DuPont.

2. Laminate preparation

The size of the specimens required for ASTM Test D790 for flexural strength was a beam 0.125 inch thick, 0.5 inch wide, and a minimum of 2.5 inches long. The thin cut films described previously were laminated in a heated press to produce a sample of the desired 0.125 inch in thickness. Control samples of the PLA films and laminates containing carbon fibers were prepared at 80 °C. Subsequent test samples were prepared by cutting PLA and fiber- or fabric-impregnated PLA films into 3 x 0.5-in. pieces and placing them in alternate layers in a heated press at 65 °C under pressure until they completely fused to form a laminate structure.

The flexural properties of fiber-reinforced materials are highly dependent upon the amount of fiber that is added to the polymer. To determine the optimum level of carbon fabric needed in the PLA composites, we prepared laminates which contained 43, 55, 57, and 67% of carbon. These laminates were fabricated by varying the number of carbon layers and PLA layers used to form the laminate.

b. Biodegradable fiber reinforcement

The best fiber reinforcement for a biodegradable polymeric implant would also be biodegradable; thus, we examined the use of an absorbable fiber system. Fibers of polyglycolide were prepared by melt spinning the resin with a ram extruder at 235 °C. Some of these fibers were drawn (oriented) and knitted into a tube. The knitted fabric was then stretched tightly over two posts and painted with several coats of a solution of PLA in methylene chloride until it was completely encapsulated in the polymer. The fabric-reinforced film was then cut free of the posts and dried in vacuo. The resulting film was far more flexible than a film of PLA alone. We did not prepare any laminates from this film due to lack of reinforcement from its high extensibility.

Because the knitted fabric was too flexible for reinforcement, fiber reinforcement was examined. Dexon sutures, consisting of high-strength braided PGA fibers, were obtained commercially in thirty-inch lengths. The sutures were tied together to produce one continuous braid, and then wrapped around two posts which were 3 inches apart. Each layer of fibers were completely encapsulated with a solution of PLA in methylene chloride. The film was then cut free of the posts and dried in vacuo. These films were firm and were then laminated at 45 °C into plates using the method described for lamination of the carbon samples. The reduced temperature was required in order to remain below the glass transition temperature of the PGA fibers. At this temperature the fibers would have undergone a phase transition which would have allowed them to relax and thereby lose the strength that was gained from the drawing process. Laminates containing suture fibers were prepared with the fibers running in the longitudinal direction (along the 3-inch length of the sample) such that the fibers would be broken by the flexural strength test. Samples of laminated, PGA-reinforced DL-PLA were also oriented by drawing the samples on a heated platen to 1.2 X. These samples were more firm and rigid than were undrawn samples.

3. Determination of flexural properties

The determination of flexural strength was carried out in accordance with ASTM Procedure D790 "Flexural Properties of Plastics" - Method I. This test was designed for rigid or semi-rigid materials that broke or ruptured before a maximum strain of 5% was reached in the outer surface of the samples. A three-point loading system utilizing center loading on a beam resting on two supports set 2 inches apart was affixed to a tensile testing machine. The samples were subjected to an increasing deflection at a rate of 0.02 inch per minute. The flexural strength, S, and the tangent modulus of elasticity, E_B, were calculated according to the following equations:

$$S = 3PL/2bd^2$$

and: $$E_B = L^3m/4bd^3$$

where: S = stress in the outer surfaces at midspan,
P = load at a given point on the load-deflection curve,
L = support span,
b = width of beam,
d = depth of beam,
E_B = modulus of elasticity in bending,
m = slope of the tangent to the initial straight-line portion of the load-deflection curve, force/instrument of deflection

Our procedures for testing the bone plate samples were identical to those used by other investigators who had previously supplied USAIDR with polymer specimens. The results should be directly comparable.

4. Results of flexural tests

The DL-PLA samples prepared by injection-molding demonstrated the effects of molecular weight upon flexural properties. Although the values were different, the same relationship was illustrated by flexural tests on DL-PLA laminates. These results, given in Table II, show that higher-molecular-weights did not improve the flexural properties of PLA polymers. In fact, the higher-molecular-weight polymers gave laminates with lower flexural properties than those of the low-molecular-weight materials. Because we used amorphous DL-PLA in our laminates, the only resistance to bending was derived from intramolecular and intermolecular forces with no crystallinity effects. The longer polymer chains in the high-molecular-weight materials with their interchain entanglements allowed the material to bend and flex more before breakage. Thus, higher molecular weights in amorphous polymers yielded tougher materials with the ability to flex and absorb impact, but they did not improve the rigidity and resistance to bending forces.

In our lamination process, we detected differences in flexural properties of PLA films cast from different solvents. Films cast from poorer solvents gave laminates with better mechanical properties as shown in Table III. Dioxan was a better solvent for PLA than 1,1,1-trichloroethane because the inherent viscosity of the PLA material in dioxane was 1.28 dL/g compared to a value of 0.88 dL/g in 1,1,1-trichloroethane. Apparently the poorer solvation diminished the extent of coiling and interchain entanglement with a resultant increase in density and modulus.

TABLE II. EFFECT OF MOLECULAR WEIGHT ON FLEXURAL PROPERTIES OF PLA

Fabrication method	Initial inherent viscosity, dL/g	Flexural strength x 10^3 psi	Modulus of elasticity x 10^6 psi
Melt-injection	0.45	6.9	1.73
Melt-injection	1.30	10.5	0.48
Spin-casting	1.33	5.8	0.27
Spin-casting	1.60	2.8	0.14

TABLE III. EFFECT OF SOLVENT ON MECHANICAL PROPERTIES OF POLY(DL-LACTIDE)

Inherent viscosity, dL/g		Casting solvent	Flexural strength x 10^3 psi	Flexural modulus x 10^6 psi
Initial	Final			
1.33	1.28	Dioxane	5.8	0.27
1.33	--	TCE[a]	7.1	0.31
1.30	0.76	Melt	10.5	0.48

[a]TCE = 1,1,1-trichloroethane

Nonresorbable fiber reinforcement of PLA samples gave the most significant improvement in flexural properties. The test results for reinforced samples are presented in Tables IV and V. As evident from the data shown in Table IV, the percentage of carbon in the laminate was critical in obtaining high flexural properties. A value of 55% by volume carbon in the laminate appeared to be the optimum level for reinforcement. Too much carbon fiber in the laminate showed the same detrimental effect upon flexural properties as too low a level. Based upon these data, we fabricated all subsequent samples with the optimum level of 55% of carbon fiber reinforcement. The addition of 11% of carbon fabric in the form of one layer of carbon weave in the center of the laminate had little effect on the modulus, although it did improve the flexural strength. The modulus was similar to the control sample because a beam under a three-point load experiences the most stress on the outside faces where it is being compressed or stretched to the greatest degree. Theoretically, the middle of the beam experiences no stress; so as expected, placement of the carbon weave in the center did not improve the modulus. However, the flexural strength of this sample was increased because of the higher tensile strength of the carbon fibers which were broken in the test. The addition of 55% of carbon fabric in the form of alternating layers of carbon weave films and PLA films resulted in dramatic increases in both the flexural strength and modulus. The flexural strength value represents a 460% improvement over the control; while the modulus value shows an improvement of 690%. In this sample, the reinforcing carbon fibers were located at points of high stress and thus gave the expected improvement in properties.

To determine the effects of lamination pressure on the composite, we prepared laminates under various pressures. These results indicated that increasing the pressure provides for better coating of the fiber, however, more and more polymer is pressed from the ends of the mold as the pressure increases. Ultimately, this increases the carbon loading above the 55% loading desired, thereby reducing the strength of the composite. To alleviate this problem, a closed-end mold was tooled. This mold prevented the loss of matrix polymer while allowing excess polymer to escape. Composites fabricated using this mold yielded the desired results.

The data in Table IV illustrates the effect of pressure on the mold during the lamination process. The open mold with a low pressure gave laminates with better flexural strength than those produced in open molds with high pressures. As before, the higher pressure on the open molds forces the PLA material out of the laminate and yields a composite with a higher level of carbon than desired.

The properties of the laminates produced with low mold pressure are not affected by the type of mold used in the lamination. However, the properties of the laminates produced with high pressure are significantly influenced by the type of mold as shown by the 55% carbon-loaded samples. The values of flexural strength and flexural modulus determined with the laminate containing 55% carbon made in the closed mold with high pressure was comparable to the 55% carbon loaded sample laminated with low pressure in the open mold.

The results obtained with the Dexon sutures recorded in Table V were not as encouraging as those obtained with the carbon fibers. Because the braided sutures will extend to some length before they become taut, at which point,

TABLE IV. FLEXURAL PROPERTIES OF CARBON-REINFORCED POLY(DL-LACTIDE) LAMINATES

Reinforcement Material	Loading, %	Pressure on mold	Type of mold	Flexural strength, x 10^3 psi	Flexural modulus, x 10^6 psi
Control	0	Low	Open	5.8	0.27
Carbon	11	Low	Open	7.5	0.27
Carbon	55	Low	Open	27.0	1.83
Carbon	57	Low	Open	20.6	0.78
Carbon	43	High	Open	14.6	0.56
Carbon	55	High	Open	18.0	0.92
Carbon	57	High	Open	13.7	1.09
Carbon	67	High	Open	8.4	0.49
Carbon	57	Low	Closed	18.6	0.79
Carbon	55	High	Closed	26.2	1.20

TABLE V. FLEXURAL PROPERTIES OF DEGRADING YARN-REINFORCING POLY(DL-LACTIDE) LAMINATES

Reinforcement Material	Loading, %	Pressure on mold	Type of mold	Flexural strength, x 10^3 psi	Flexural modulus, x 10^6 psi
Control	0	Low	Open	5.8	0.27
PGA sutures oriented	50	Low	Closed	2.3	0.9
PGA sutures	50	Low	Closed	4.1	0.20
PLA-oriented	0	Low	Open	9.9	1.o6

they elongate, the test specimens containing the Dexon sutures did not break. To obtain reinforcement with the sutures, it would be necessary to remove all the extension or elongation in the fibers.

Orientation of the PLA samples by hot drawing increases the modulus of elasticity as shown in Table V. In breaking the control sample, little resistance is encountered to bending under the three-point load because the strain is absorbed by the chains as they straighten out. Orientation of the samples "pre-straightens" the chains and provides increased resistance to any further bending. Therefore, a high modulus is obtained although the flexural strength is similar to the unoriented control.

Due to difficulties in preparing samples, we modified the procedure for the use of open molds to obtain high-strength composites. In the improved procedure, alternate layers of PLA and fibrous-reinforced PLA are fused one layer at a time in a press at 70-75 °C and 2,000-3,000 psi. At the temperatures and pressures employed in the improved procedure, we encountered only minor amounts of composite flashing or spreading.

The flexural properties of the fibrous-reinforced composites are given in Table VI, along with the polymer inherent viscosity, the sample thickness, and the force required to bend the sample to its breaking point. The data in Table VI support several important hypotheses and conclusions. First, the continuous-filament yarns yielded composites with higher flexural properties than those with fabric reinforcement. 100% of the fibers, when longitudinally arranged, provide reinforcement, whereas, fabrics, because of their biaxial fiber arrangement, provide only partial reinforcement. In addition, the flexural properties of these fiber-reinforced composites were superior to that of bone and equivalent to the target values established in our research proposal. These materials were not completely biodegradable, however, and served only as a model for designing systems with sufficient strength and rigidity.

A second conclusion confirmed by the data in Table VI is that within the range studied, higher-molecular-weight PLA does not yield composites with improved initial flexural properties. In fact, the lower-molecular-weight PLA (0.58 dL/g IV) gave a composite with carbon fabric which displayed better flexural strength than a similar composite with PLA of higher molecular weight (1.14 dL/g inherent viscosity). This same result was seen in our earlier tests with non-reinforced PLA samples. Apparently, the long chains of the high-molecular-weight polymer provide more flexibility due to entanglement with adjacent chains, whereas the shorter chains afford greater rigidity.

A third fact emphasized in Table VI is that the values of flexural strength and flexural modulus are independent of the sample thickness since that value has been used in the calculations to derive the flexural properties. However, the load or force required to break the sample is a function of sample size. Thus, although the ceramic and carbon yarn composites have almost identical flexural properties, the ceramic yarn composite with a thickness of 0.159 in. will resist at least twice the force before breaking of the carbon yarn composite with a thickness of only 0.109 in.

TABLE VI. FLEXURAL PROPERTIES OF FIBROUS-REINFORCED POLY(DL-LACTIDE) LAMINATES

Fiber	Polymer viscosity, dL/g	$\bar{L}$,[a] lb	$\bar{S}$,[b] x 10^3 psi	$\bar{E}$,[c] x 10^8 psi	Sample thickness, in.
Nextel 312 Ceramic yarn	1.14	119.6	28.4	1.8	0.159
Nextel 312 Ceramic fabric	1.14	24.1	11.6	1.3	0.116
Thornel 300 Carbon yarn	1.14	48.8	24.3	1.7	0.109
Rayon VCL Carbon fabric	1.27	27.5	12.7	0.6	0.115
Rayon VCL Carbon fabric	0.58	33.8	20.9	0.8	0.102

[a] Average breaking load.

[b] Average flexural strength.

[c] Average flexural modulus.

5. Property retention: in vitro test results

Because the fibrous-reinforced laminates possessed satisfactory initial flexural properties, we then evaluated the retention of these properties in vitro. The fibrous-reinforced laminates were exposed to a phosphate-buffered saline solution (0.2 M, pH 7.4) at 37 °C for 2, 4, 6, and 8 weeks to simulate conditions in vivo. After the appropriate exposure time, the samples were removed, blotted dry, and conditioned for 24 hours in a room with controlled temperature and humidity. The conditioned samples were then tested for flexural properties.

The results of these studies are shown in Tables VII-IX. The flexural strength and flexural modulus values are also presented graphically in Figures 3 and 4. As expected, the data from our tests showed a decrease in flexural properties of the samples with their exposure to the saline solution. However, the rate of decrease in properties with the samples prepared with carbon fabric and ceramic yarns was very rapid. The carbon fabric-reinforced samples had only marginal flexural strength and flexural modulus values initially, and within two weeks the flexural properties of these samples degraded to unacceptable values. The ceramic yarn-reinforced samples had superior values of flexural properties initially, but within four weeks, these values had decreased to marginal levels.

The thinner samples of ceramic yarn-reinforced PLA, identical to those sent to the Army for in vivo tests, provided better retention of properties. Even after eight weeks, the thinner samples yielded excellent values of flexural strength and flexural modulus. The improved retention of properties was probably due to improvements in lamination with the thinner samples.

As mentioned earlier, the flexural properties are independent of the sample thickness, but the load required to break the samples is proportional to the thickness of the plate. Thus, the thicker samples of ceramic yarn-reinforced materials even after 8 weeks of exposure required almost twice the force to break as the thinner samples. These values are shown in Tables VIII and IX.

6. Further reinforcement with carbon and ceramic yarns

As a result of the test data presented in the previous sections, we then evaluated the carbon and ceramic yarn reinforcement effects of polymers with low-(IV=0.67 dL/g) and medium-molecular-weight (IV=1.04 dL/g) respectively.

The fiber-reinforced composites were prepared by the same general procedure as described previously. Films of PLA with the appropriate viscosity values were fabricated and then laminated with fiber-reinforced films of the same polymer. The reinforcing fibers consisted of either carbon or ceramic materials.

As reported previously, we were able to obtain high-strength composites using our open-mold lamination procedure. Because initial animal experiments conducted by the Army suggested that we needed thinner composite plates, we prepared the new composites with four layers of fiber-reinforced film and three layers of PLA film.

TABLE VII. RETENTION OF FLEXURAL PROPERTIES FOR CARBON FABRIC-REINFORCED LAMINATES

Exposure[a] time, days	$\bar{L}$,[b] lb	$\bar{S}$,[b] x 10^3 psi	$\bar{E}$,[b] x 10^6 psi	Sample thickness, in.
0	75.4	15.0	0.8	0.182
14	46.2	9.8	0.5	0.172
28	51.2	8	0.5	0.193
42	43.9	7.0	0.4	0.207
56	33.7	3.9	0.3	0.214

[a] Phosphate-buffered saline solution at 37 °C.

[b] See Table II for explanation.

TABLE VIII. RETENTION OF FLEXURAL PROPERTIES FOR CERAMIC YARN-REINFORCED LAMINATES

Exposure[a] time, days	$\bar{L}$,[b] lb	$\bar{S}$,[b] x 10^3 psi	$\bar{E}$,[b] x 10^6 psi	Sample thickness, in.
0	129.3	39.6	2.5	0.143
14	71.5	19.4	1.5	0.153
28	50.2	12.2	0.8	0.172
42	52.6	11.3	1.1	0.175
56	54.0	10.9	1.2	0.180

[a] See Table III for explanation

[b] See Table II for explanation.

TABLE IX. RETENTION OF FLEXURAL PROPERTIES FOR THINNER CERAMIC YARN-REINFORCED LAMINATES

Exposure[a] time, days	$\bar{L}$,[b] lb	$\bar{S}$,[b] x 10^3 psi	$\bar{E}$,[b] x 10^6 psi	Sample thickness, in.
0	27.1	31.3	2.5	0.078
14	33.7	26.5	2.4	0.094
28	29.4	24.9	2.3	0.095
42	27.3	23.8	2.2	0.090
56	28.0	23.7	2.0	0.092

[a] See Table III for explanation.

[b] See Table II for explanation.

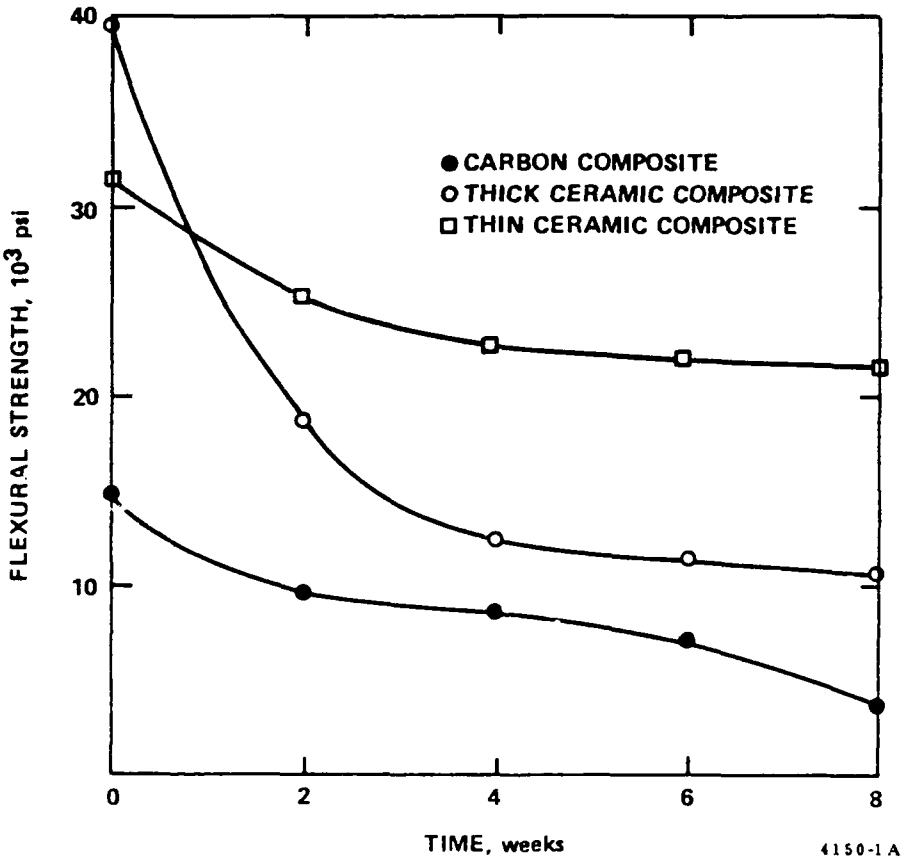


Figure 3. Effect of in vitro exposure on flexural strength values.

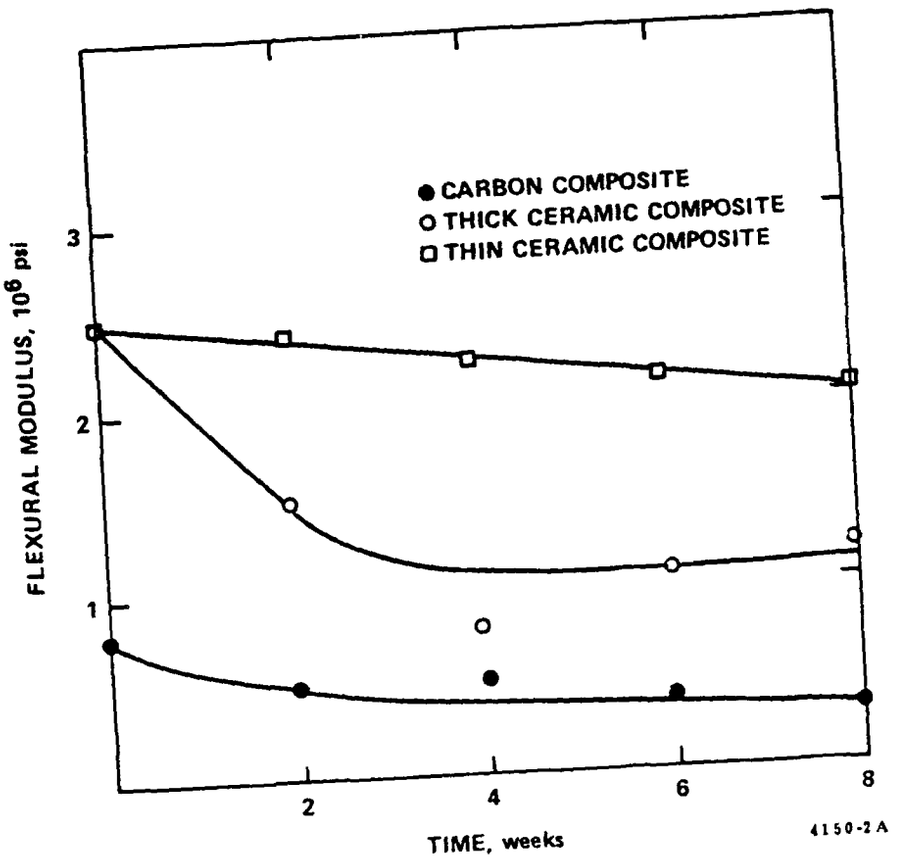


Figure 4. Effect of in vitro exposure on flexural modulus values.

7. Determination of flexural properties of yarn-reinforced materials

The fiber-reinforced laminates with PLA were tested for flexural strength and modulus according to ASTM D-790 as described in Section III.B.3. The results of these tests are given in Table X with data also on the inherent viscosity of the polymer, the sample thickness, and the force required to bend the sample to its breaking point. Studies to determine the retention of properties in vitro were also conducted.

a. Initial evaluation of laminated plate

From the data in Table X, we see that the composites reached preproposed target values for PLA bone plates of 20,000 psi for flexural strength and 2 X 10^6 psi for flexural modulus. The values obtained with the low-molecular-weight PLA and carbon fiber composite are much higher than required. As expected, the low-molecular-weight PLA gave composites with higher values of flexural properties. However, the major factor in composite strength appears to be the type of reinforcing fiber. The carbon fiber gave laminates with the highest values of flexural properties followed by the ceramic fiber laminates. A possible explanation for these results may be derived from the tensile properties of the various fibers as shown in Table XI. The tensile strength of the carbon fiber yarn is greater than that for the two ceramic fibers. In fact, the flexural properties of the composites tend to compare in relative order with the tensile strengths of the fibrous reinforcement. Tensile modulus values of the reinforcing fibers do not appear to be as important for composite properties as do the tensile strength values. This fact is illustrated by both Thornel 50 and Fiber FP having essentially the same tensile modulus values, but the flexural properties of composites from these two materials are quite different.

Although the flexural properties of the PLA composites tend to correlate with the tensile-strength values of the reinforcing fibers, another factor may be responsible for some of the observed differences. Some of the high-modulus reinforcing fibers are coated with an organic polymer known as a sizing agent, and used to improve the compatibility and wettability of the fibers to impregnating resins. Thus, the Thornel 50 yarns contain an acrylic size, the Nextel AB 312 fibers normally contain either an acrylic or polytetrafluoroethylene size, and the Fiber FP yarn contains a small amount of silica size. The size on the reinforcing fiber probably influences the adhesion of the polymer to the fiber with resultant changes in flexural properties.

b. In vitro evaluation of laminated plates

The fiber-reinforced PLA composites prepared with low- and medium-viscosity polymers were also subjected to in vitro degradation tests. Degradation studies on control samples with no fiber reinforcement were also conducted. For the degradation studies, we employed a phosphate-buffered saline solution (0.2 M, pH 7.4) at 37 °C. Samples were removed after 2, 4, 6, and 8 weeks and tested for retention of inherent viscosity and flexural properties. All samples were dried at 70 °C overnight and conditioned in a constant-temperature (23 °C) and constant-humidity (35% RH) room before being broken in the standard flexural test. For viscosity measurements, we dissolved the samples in dichloromethane, filtered the solution to remove the reinforcing fibers, and evaporated the dichloromethane under conditions of

TABLE X. FLEXURAL PROPERTIES OF FIBER-REINFORCED LAMINATES FROM LOW- AND MEDIUM-VISCOSITY MATRIX POLYMER

Fiber	Polymer viscosity, dL/g	$\bar{L}$,[a] lb	$\bar{S}$,[a] x 10^3 psi	$\bar{E}$,[a] x 10^6 psi	Sample thickness, in.
Nextel AB 312	1.04	77.7	23.5	1.3	0.161
Nextel AB 312	0.67	27.2	27.5	2.0	0.083
Thornel 50	1.04	144.7	25.3	1.6	0.215
Thornel 50	0.67	61.1	47.9	5.7	0.091
DuPont Fiber FP	1.04	58.3	10.1	1.1	0.215
DuPont Fiber FP	0.67	62.5	14.1	1.5	0.170

[a]See Table II for explanation.

TABLE XI. MECHANICAL PROPERTIES OF REINFORCING FIBERS

Fiber	Tensile strength, x 10^3 psi	Tensile modulus, x 10^6 psi
Thornel 50	320	57
Nextel AB 312	250	22
Fiber FP	200	55

heat and vacuum. This procedure not only served to remove fibers, but it also ensured a more homogeneous sample for viscosity measurements. The inherent viscosity of the polymer was then measured in chloroform at 30 °C.

The results of the degradation studies for low- and high-molecular-weight samples are presented in Figures 5-10. These figures show the same decrease in flexural properties with exposure time as observed for other composites. The loss in flexural properties of the composite was assumed to result from hydrolytic degradation of the polymer, which lead to delamination of the films or voids in the composite. These voids created cracks and weak spots in the laminate with a subsequent loss in strength.

The viscosity losses shown in the figures followed the expected behavior. We obtained an almost linear decrease in viscosity during the first several weeks, but the rate of decrease slowed, for initially high-molecular-weight material, during the last weeks as lower-molecular-weight polymer was formed. Hydrolysis of the long molecular chains of higher-molecular-weight polymer leads to the short chains of lower-molecular-weight polymer with a rapid decrease in viscosity. This effect becomes less pronounced with hydrolysis of the shorter polymer chains.

During the in vitro degradation studies, we also determined the weight loss of the exposed samples after two, four, six, and eight weeks. These results agree with those of other investigators who found very little weight loss with PLA until the polymer had degraded to a material with such low molecular weight as to be water soluble.

Even though the three fibers used for reinforcement in these samples are not biodegradable, the degradation study shows the gradual loss of flexural strength and modulus of elasticity, which may be expected in any fiber-reinforced system with PLA. This degradation, producing a gradual loss of laminate strength, will permit an increasing transfer of load to the developing bone. The gradual load transfer to the newly forming bone will result in considerably stronger bone scaffolding by reducing "stress-protection" atrophy.

Our in vitro data indicated that satisfactory flexural properties were maintained for four to six weeks. After this period, new bone should have formed, and it should be able to support part of any external load. Preliminary evidence from the in vivo study in canines conducted by the Army with these fiber-reinforced biodegradable plates showed good bone growth and stability.

C. Selection of Sterilization Procedure

The PLA composites were to be sterilized before use as mandibular cribs. Sterilization by gamma irradiation or ethylene oxide appeared to be the only methods available because steam autoclaving caused a significant degradation of the polymer. Typically, gamma irradiation has been used for the sterilization of PLA microcapsules produced in our laboratories. The effect of irradiation on the load-bearing character of PLA polymer, however, had not been determined. Therefore, we used both ethylene oxide and gamma irradiation to

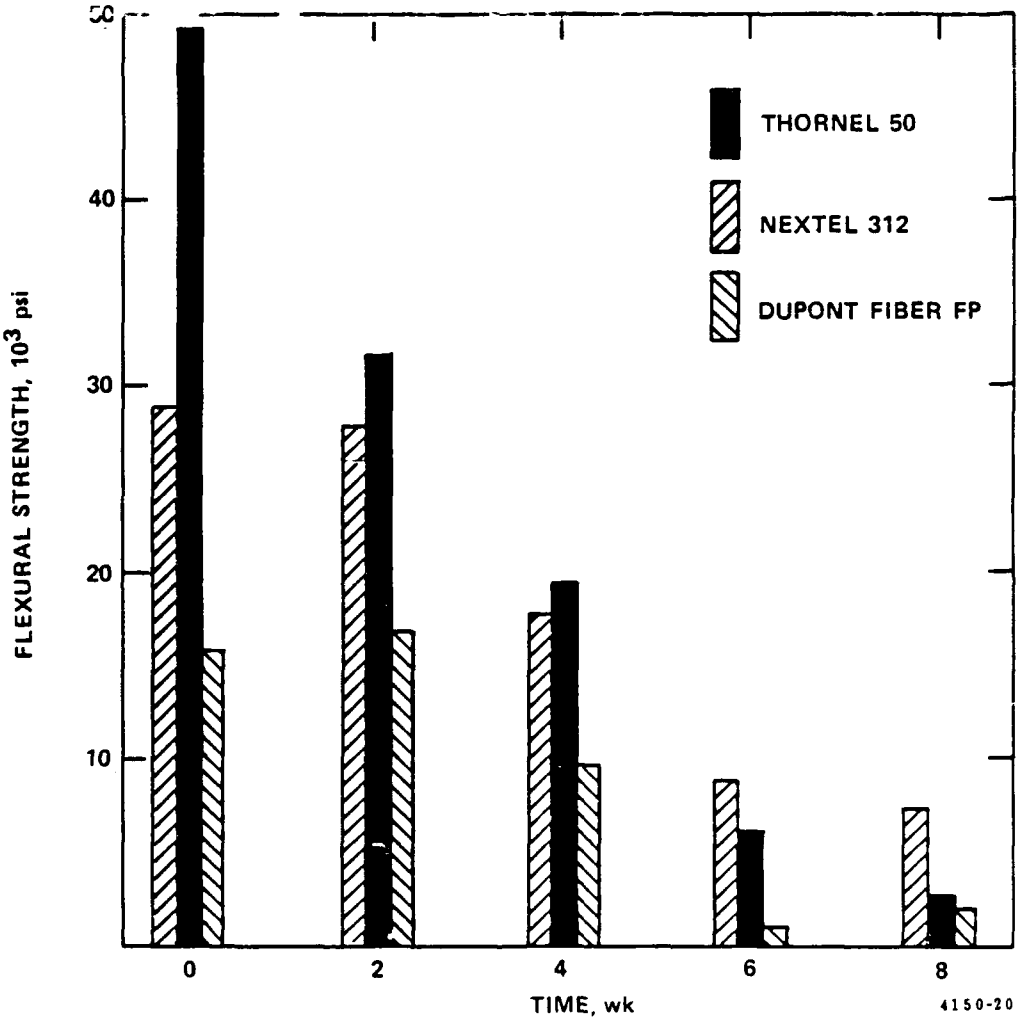


Figure 5. Effect of in vitro exposure on flexural strength of fiber-reinforced low viscosity PLA laminates.

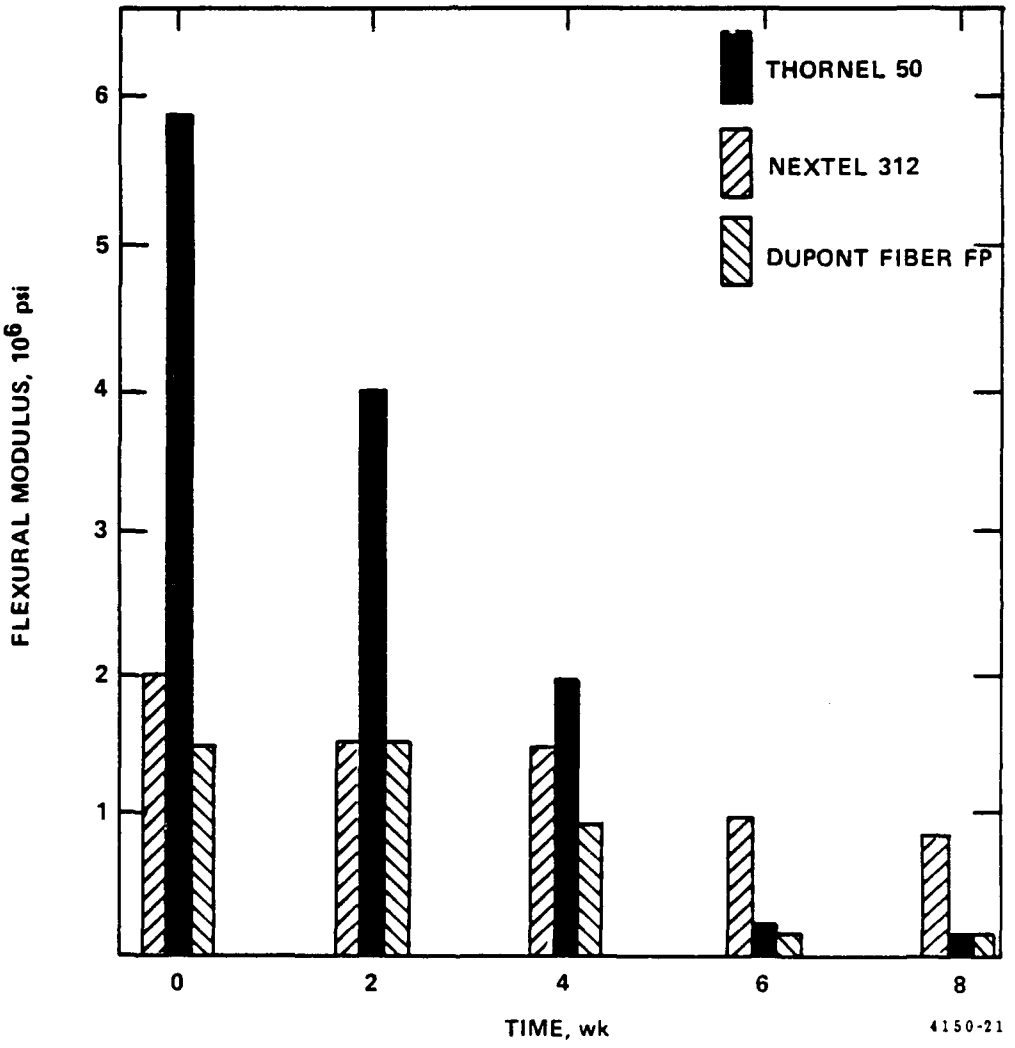


Figure 6. Effect of in vitro exposure on flexural modulus of fiber-reinforced low-viscosity DL-PLA laminates.

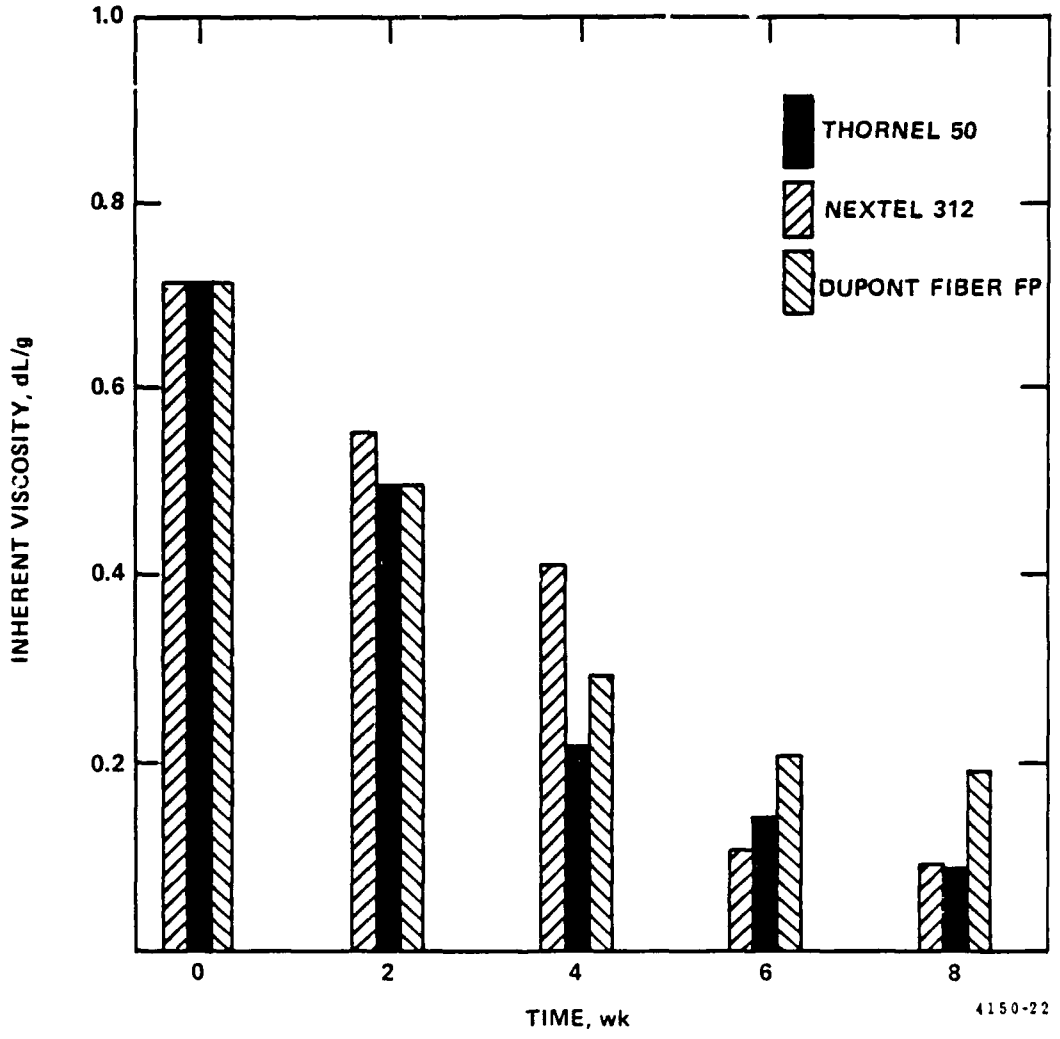


Figure 7. Effect of in vitro exposure on inherent visocisity of low-molecular-weight PLA laminates.

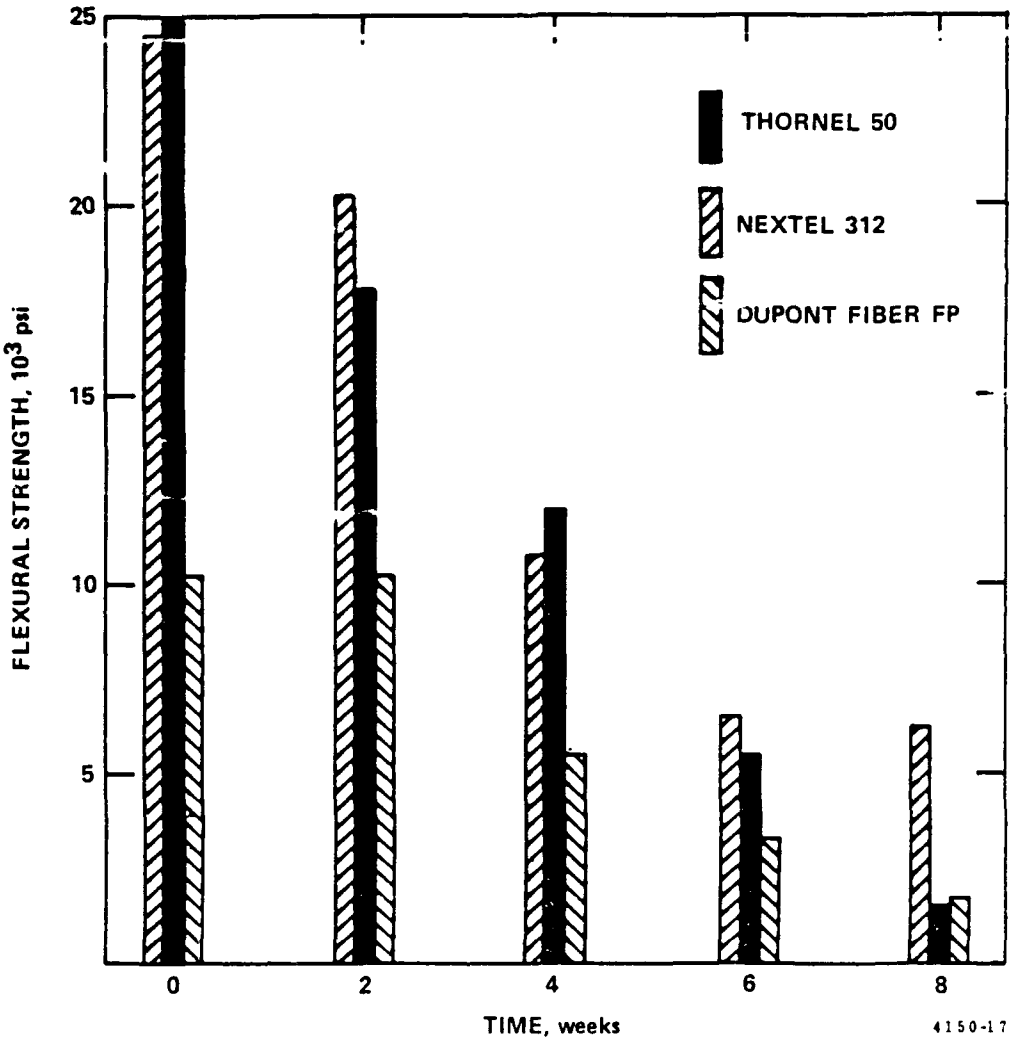


Figure 8. Effect of in vitro exposure on flexural strength of fiber-reinforced high-viscosity PLA laminates.

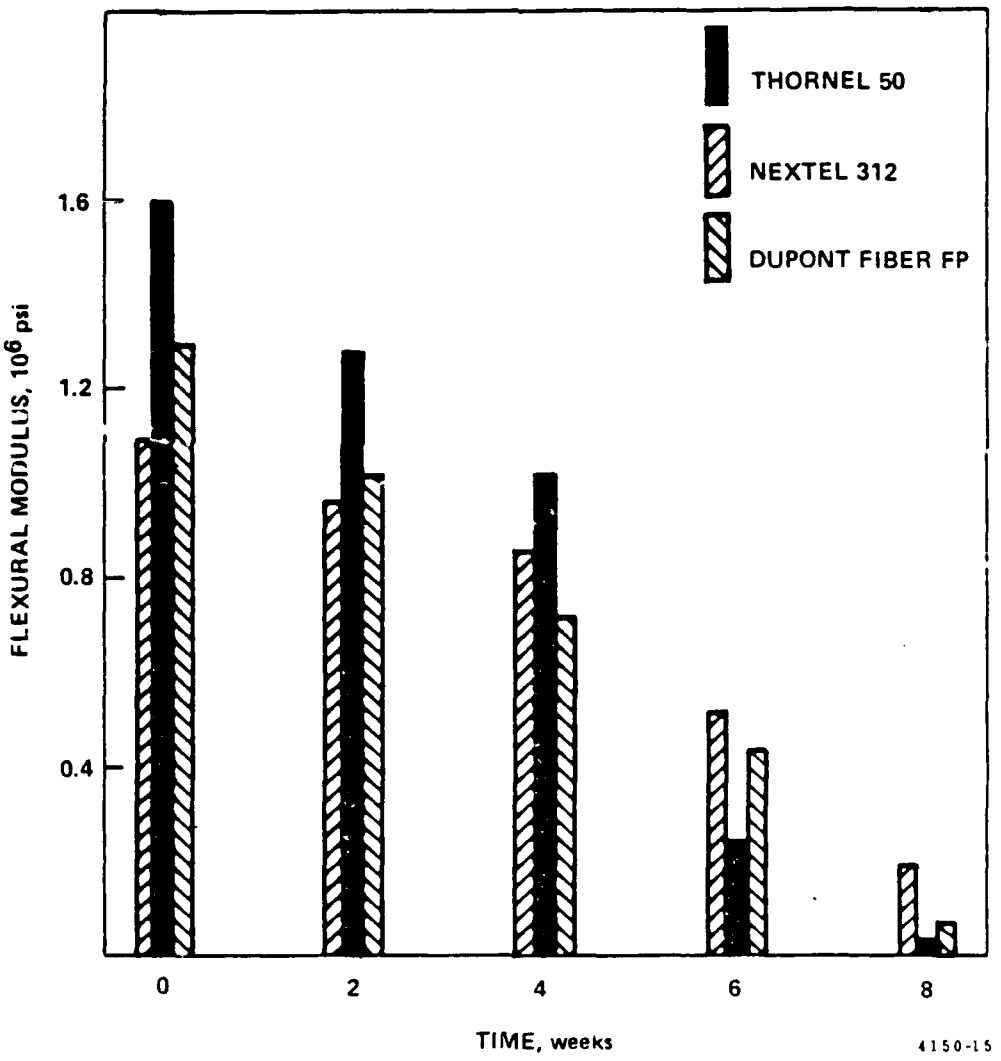


Figure 9. Effect of in vitro exposure on flexural modulus of fiber-reinforced high-viscosity PLA laminates.

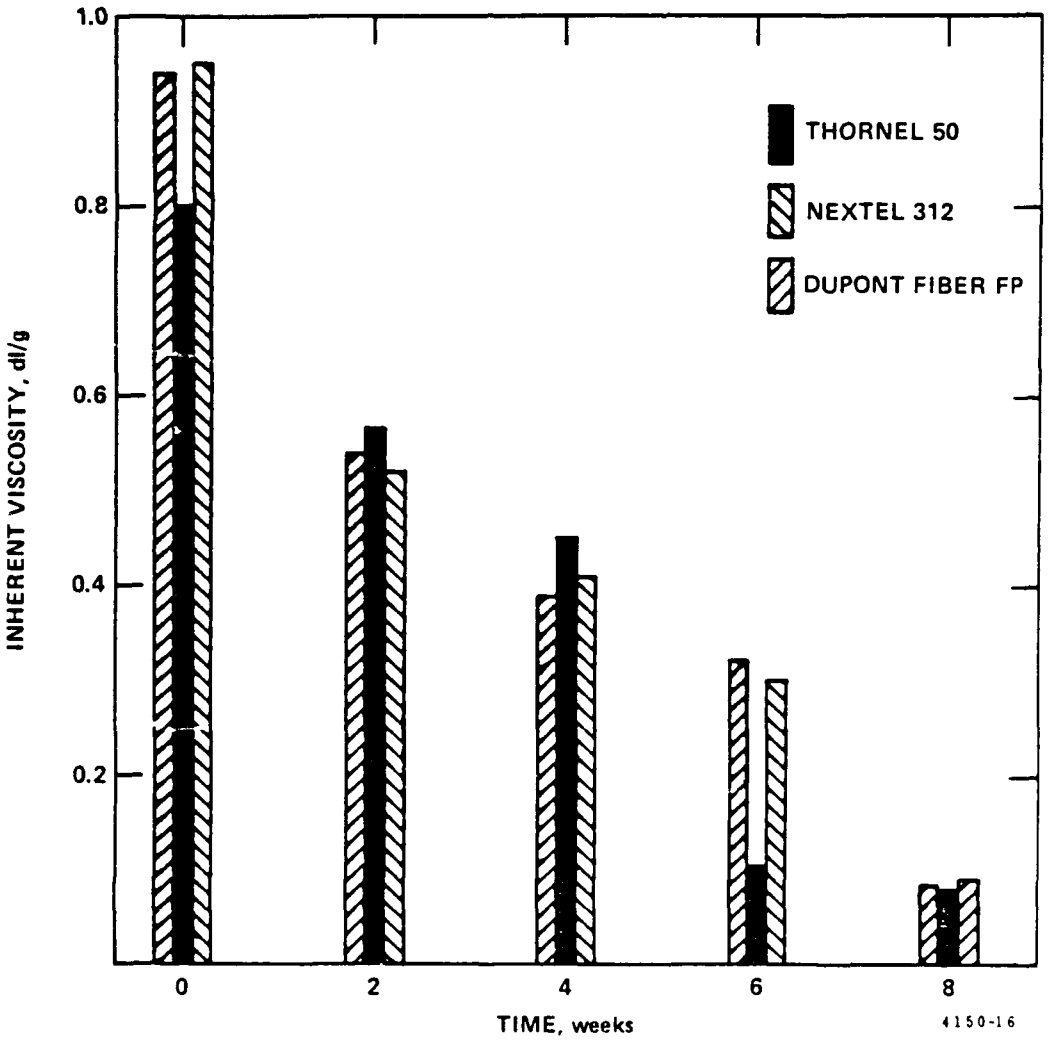


Figure 10. Effect of in vitro exposure on inherent viscosity of fiber-reinforced high-viscosity PLA laminates.

sterilize composites containing PLA with viscosities of 0.67 and 1.04 dL/g to determine which procedure was the more acceptable.

The gamma-irradiation sterilization consisted of an exposure of the composite plates to 2.0 megarads of irradiation from a cobalt-60 source. Ethylene oxide sterilization was achieved by exposure of the samples to ethylene oxide for three hours at 60 °C. The sterilized samples were then tested for retention of flexural properties and inherent viscosity. The results of these tests show a greater loss in polymer viscosity with gamma-irradiation than with ethylene oxide sterilization in Tables XII and XIII. Apparently the irradiation caused chain clevage of the polymer. With ethylene oxide exposure, we observed essentially no loss in polymer viscosity. However, both sterilization methods decreased the flexural properties of the composites. Based upon the results of these tests, we recommend ethylene oxide as the preferred method for composite sterilization.

D. Preparation of Plates for the Army's Canine Mandibular Repair Study

We prepared samples of fiber-reinforced laminates for evaluation by the Army in a canine implant study concerned with the repair of mandibular fractures. The Army reported that in earlier mandibular repair experiments with polylactic acid materials, the polymeric bone plates warped to such extents that they actually pulled the bone screws away from the mandible. We developed methods for preventing the warpage, and we examined harvested plates for retention of initial properties and material integrity.

1. Prevention of warpage

For our initial samples of mandibular cribs, we prepared samples of ceramic yarn-reinforced PLA, applied heat, and bent them around a rod to obtain the desired curvature. In vitro studies showed that the cribs almost completely opened up after only 2-4 days of exposure. Apparently, residual stresses were induced in the crib during the bending operation, and upon exposure to heat, the sample tended to return to its original configuration to relieve these built-in stresses.

To avoid this warpage of the cribs, we annealed several samples. The process of annealing, commonly used with polymers and glass, consists of heating the material above the glass-transition temperature of the polymer in its bent shape for extended periods to relieve the residual stresses. The results of our annealing experiments, as shown in Table XIV, indicate a significant decrease in warpage. Two samples which were bent into cribs and annealed for 16 hours were sent to the Army for in vivo testing in dogs.

We also used another method to prevent warpage of the sample cribs. Samples were prepared with a process whereby two reinforced plates were connected with a flexible hinge of PLA polymer. Because the film of PLA used as the hinge or bent portion of the crib was quite thin, it did not have sufficient strength to warp the two reinforced plates even if slight stresses are generated during the bending operation. Six mandibular cribs fabricated in this fashion were sent to the Army for in vivo testing.

TABLE XII. EFFECT OF STERILIZATION ON HIGH-VISCOSITY POLYLACTIDE COMPOSITES

Composite	Retention of Properties after Sterilization, %					
	Gamma irradiation			Ethylene oxide		
	$\bar{S}$[a]	$\bar{E}$[a]	IV[b]	$\bar{S}$	$\bar{E}$	IV
Nextel 312	68	54	71	105	100	100
Du Pont Fiber FP	86	100	70	95	100	94
Thornel 50	92	75	73	80	56	101

[a] See Table II for explanation.

[b] Inherent viscosity.

TABLE XIII. EFFECT OF STERILIZATION ON LOW-VISCOSITY POLYLACTIDE COMPOSITES

Composite	Retention of Properties after Sterilization, %: Gamma irradiation $\bar{S}$[a]	$\bar{E}$[a]	IV[b]	Ethylene oxide $\bar{S}$	$\bar{E}$	IV
Nextel 312	64	50	75	58	45	95
Du Pont Fiber FP	100	107	86	83	80	109
Thornel 50	62	32	81	84	57	102

[a] See Table II for explanation.

[b] Inherent viscosity.

TABLE XIV. EFFECT OF ANNEALING ON STABILITY OF MANDIBULAR CRIBS

Exposure[a] time, days	Separation between plates, in.		
	Control	Annealed 4 h	Annealed 7 h
1	0.615	0.745	0.545
2	0.826	0.843	0.580
4	open	0.855	-
5	-	0.857	-
6	-	-	0.695
7	-	0.857	0.695
11	-	0.880	-
21	-	0.940	0.890

[a]See Table III for explanation.

2. Evaluation of plates harvested from canine implant study

During the third year of the contract, we received three dog mandibles from USAIDR. These mandibles had been fractured and repaired with bone plates that we had supplied to the Army. The plates comprised PLA reinforced with Nextel 312, a nonbiodegradable ceramic fiber. The mandibles represented in vivo test periods of 3, 8, and 12 weeks. The polymeric bone plates were removed from the dog mandibles, and standard flexural test and molecular-weight determinations were performed.

Prior to their flexural testing, samples were dried. Following the flexural testing, polymer and ceramic fibers were separated by dissolution and filtration. The IV of this polymer was then determined. Results are shown in Table XV.

The in-vivo data correlated with our in-vitro tests in that there was a loss with time of both flexural strength and flexural modulus. There is also a corresponding decrease in the inherent viscosity of the PLA. The viscosity values from the in vivo samples were somewhat higher than those obtained in the in vitro evaluations. This was believed to have resulted from the degree of exposure to the test media.

Although the flexural properties of the in-vivo plates show the same trend with time as those of the in-vitro samples, the values are significantly different. The values of the flexural properties for the in vivo plates are lower by a factor of at least 10 than those of the in-vitro samples. Because the polymer viscosities and molecular weights of both samples are approximately the same, we concluded that the lower flexural properties of the in-vivo samples are were due to differences in the polymers.

One possible explanation for the lower flexural values was that sterilization of the plates prior to testing affected the in-vivo degradation. Our in-vitro degradation studies were conducted on nonsterilized samples, while the plates recovered from the dogs had been sterilized by gamma irradiation before implantation. It was previously shown that 40% of the flexural properties of Nextel 312 ceramic fiber-reinforced plates were lost after exposure to gamma irradiation. With this loss in properties of virgin samples with exposure to gamma irradiation, both in vitro and in vivo degradation rates of the flexural properties of the plates could have been accelerated to give the low values that we obtained from the animal studies.

E. Totally Biodegradable Fixation System

The results with the carbon and ceramic fiber-reinforced composites demonstrated that PLA plates could be fabricated with flexural properties equivalent to or greater than those of bone. Additionally, the preliminary in vivo studies by the Army with these plates in dogs indicated acceptable stability and performance. However, the carbon and ceramic fibers are not biodegradable. In order to develop a totally biodegradable fixation plate with acceptable initial properties and property retention, we investigated a number of design and fabrication modifications.

TABLE XV. PROPERTIES OF REINFORCED POLY(DL-LACTIDE) BONE PLATES AFTER IN VIVO EXPOSURE

Exposure[a] time, weeks	$\bar{S}$,[a] psi	$\bar{E}$,[b] psi	ιv,[c] dL/g in $CHCl_3$
3	1075	26,000	0.59
8	300	6,060	0.42
12	50	940	0.36

[a] Flexural strength.

[b] Flexural modulus.

[c] See Table VIII for explanation.

1. Reinforcement with biodegradable fibers

We first examined commercially available biodegradable fibers for use in reinforcing PLA plates. PGA sutures were drawn to produce high-modulus, low-elongation fibers. These were then laminated below the glass transition temperature with PLA. The results of flexural property determinations performed on these samples are shown in Table XVI.

The flexural strength of the laminates decreased, but the flexural modulus increased slightly. The flexural modulus, however, was still insufficient for use of the PGA-reinforced plates in fracture fixation. As a result, we abandoned the use of PGA suture material and turned our attention to the development of high-modulus, low-extensibility, biodegradable reinforcing fibers.

Our first attempt at obtaining high-modulus biodegradable fibers was the precipitation of polycaprolactone (PCL) from a vigorously stirred solution by addition of a nonsolvent to produce fibrils. These fibrils were highly crystalline and oriented and were collected as a nonwoven sheet. The PLA laminates produced from this sheet showed no enhancement of flexural properties. Apparently, the lamination operation destroyed the crystallinity and orientation of the polycaprolactone fibrils. We attributed this effect to the low glass-transition temperature and melting point of PCL.

A similar precipitation experiment with L-PLA from the same solvents did not yield fibrils, but rather an agglomerated mass of polymer. PGA which is a highly crystalline and high-melting biodegradable polymer did not produce fibrils suitable for lamination.

Therefore, we attempted to grow high-modulus biodegradable fibers in solution using sonic frequencies methods developed by Hughes Aircraft Company. Researchers found that sonic agitation of polymer solutions under the proper conditions could produce fibers. The resulting fibers, which were formed in a 3-D array, have outstanding tensile strength. Because the fibers are grown in situ, reinforcement occurs not only in all directions, but also in voids and crevices that would be potentially weak spots in the sample. Although we were also able to successfully produce polypropylene fibers, we were unable to grow biodegradable PGA fibers.

2. Orientation of biodegradable polymer laminates

We anticipated that orientation of non-reinforced polymer plates might serve to improve flexural properties. Orientation was achieved by a drawing process that aligned the molecular chains of the polymer. The stretched molecular chains formed regular patterns and exhibited increased rigidity due to a more ordered and crystalline structure.

Drawing of the polymer plates was performed on our materials testing machine. Two infrared lamps were used for heat sources with the draw temperature being controlled by the distance of the sample from the heat lamps. The sample of PLA was prepared by the same spin-casting process as described previously. The sample was then cut to the proper size, and the standard flexural tests were performed. The results are shown in Tables XVII and XVIII. At an optimum draw temperature near the glass-transition point, it

TABLE XVI. EFFECT OF PGA FIBER REINFORCEMENT ON LAMINATE FLEXURAL PROPERTIES

PGA FIBER REINFORCEMENT			
Level, %	Orientation	$\bar{S}$,[a] x 10^3 psi	$\bar{E}$,[a] x 10^3 psi
--	--	7.28	0.33
50	Undrawn	2.30	0.09
15	Drawn	5.60	0.37

[a]See Table II for explanations.

TABLE XVII. ORIENTATION OF L-PLA LAMINATES

Temperature, °C	Draw Ratio	$\bar{S}$,[a] x 10^3 psi	$\bar{E}$,[b] x 10^3 psi
--	--	2.56	0.02
110	2.0	4.29	0.34
150	2.0	1.79	0.11

[a]Average flexural strength.

[b]Average flexural modulus.

TABLE XVIII. ORIENTATION OF DL-PLA LAMINATES

Temperature, °C	Draw Ratio	$\bar{S}$,[a] x 10^3 psi	$\bar{E}$,[b] x 10^3 psi
--	--	2.75	0.16
60	2.7	6.03	0.20
60	4.7	7.42	0.33

[a]Average flexural strength.

[b]Average flexural modulus.

appeared that both flexural strength and flexural modulus increased as the degree of stretch was increased.

A greater change in flexural properties, particularly in modulus of elasticity, was noted for the L-PLA compared to the DL-PLA. This was a result of lamination of the more crystalline polymer. Films of L-PLA do not adhere to each other readily even at elevated temperature and pressure, and in both the orientation process and the Instron testing, delamination was a problem.

3. Injection molding of L-PLA

Due to the difficulty in laminating L-PLA, we examined injection molding as an alternative. We anticipated that injection molding of this polymer might provide better reproducibility, easier fabrication, and faster manufacture of polymeric bone plates. Also, a more uniform, homogeneous sample would possibly be obtained.

We had attempted injection molding of DL-PLA initially at the start of the project and rejected it due to problems with polymer hydrolysis. Because the presence of small amounts of moisture at the elevated injection-molding temperature caused severe molecular breakdown of the polyester structure, a much higher-molecular-weight sample would be used initially, such that the decrease in molecular weight by the injection-molding procedure would still give a satisfactory level. Because it was easier to produce, high-molecular-weight samples of L-PLA was chosen for injection molding samples.

In the injection molding of L-PLA, we used a sample with an inherent viscosity of 1.5 dL/g. Strain lines were evident in the sample molded at 205 °C. However, the sample produced at 210 °C was strong although somewhat brittle due to the crystalline nature of L-PLA.

We tested both samples in the standard flexural test, and the results of these tests as well as the final inherent viscosities are shown in Table XIX. Both the flexural strength and the flexural modulus values were increased by approximately 100% over laminated, unreinforced samples of PLA. As expected, the inherent viscosity of the polymer dropped as the molding temperature was raised, but the molecular weight of the molded polymer was still adequate for a long implant life time.

Two methods for achieving more homogeneous injection-molded specimens that were free of stress lines, were higher injection-molding temperature and annealing of the molded sample. These methods were then investigated.

Two samples, IV = 1.00 dL/g, and 0.60 dL/g, of L-PLA were injection molded at 230, 245, and 260 °C. The molded samples were then broken in the standard flexural tests. The results are shown in Table XX and Figures 11 and 12.

Data from these trials indicated that the fabrication and flexural properties of injection-molded L-PLA were largely dependent upon temperature and polymer molecular weight. The polymer flowed more easily at higher temperatures, and hence formed a plate with fewer strain lines. At very high temperatures, degradation of ester linkages in the polymer became a problem with a resultant loss in molecular weight. Mechanical properties increased

TABLE XIX. PROPERTIES OF INJECTION-MOLDED L-PLA PLATES

Temperature, °C	$\bar{S}$, psi	$\bar{E}$, psi	IV, dL/g in $CHCl_3$
205	8,900	302,600	1.2
210	11,400	398,700	1.1

TABLE XX. PROPERTIES OF L-PLA PLATES INJECTION MOLDED AT HIGHER TEMPERATURES

Molding temperature, °C	$\bar{S}$,[a] x 10^3 psi	$\bar{E}$,[a] x 10^3 psi	Initial IV[b] dL/g	Final IV dL/g
230	1.55	0.244	1.00	0.79
245	2.51	0.328	1.00	0.64
260	4.90	0.379	1.00	0.56
230	1.06	0.178	0.60	0.48
245	1.94	0.213	0.60	0.40
260	0.69	0.134	0.60	0.23

[a] See Table II for explanation.

[b] See Table VIII for explanation.

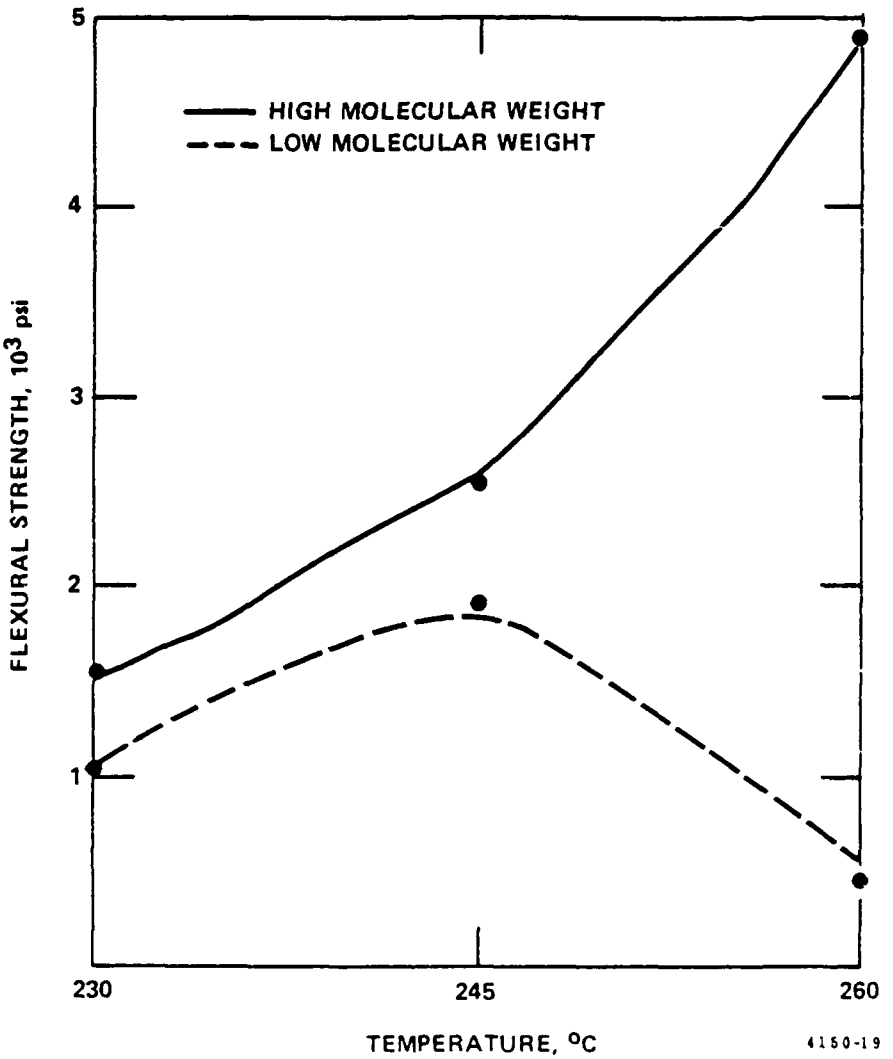


Figure 11. Effect of injection-molding temperature on flexural strength of L-PLA plates.

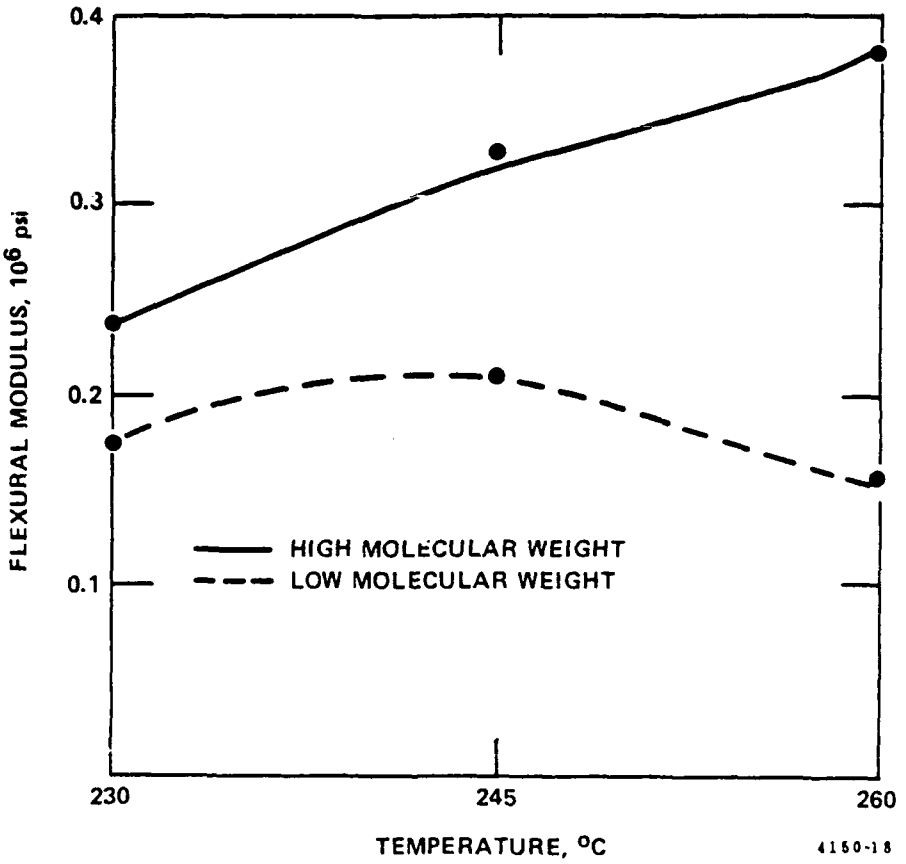


Figure 12. Effect of injection-molding temperature on flexural modulus of L-PLA plates.

with molding temperature until degradation phenomena became dominant. As the figures show, once a low value of polymer MW (low IV) was obtained by injection molding, the flexural properties decreased. As expected, polymers with lower initial molecular weight reached the break point earlier than those with higher molecular weight. Consequently, the initial molecular weight of the injection-molded polymer was critical. Figures 11 and 12 also show the flexural properties values for the L-PLA samples with an IV of 1.00 dL/g increase with molding temperature until typical values for these polymers were obtained. However, the values of flexural strength even at the higher molding temperature are less than those we noted in plates prepared from L-PLA with an initial polymer viscosity of 1.5 dL/g.

Based upon the results of the injection-molding trials, we expected that L-PLA with initial viscosity values in the 1.5-2.5 dL/g range would yield samples with high flexural strength if molded at temperatures in the 260-280 °C range. However, attempts to injection-molded L-PLA (IV=2.41 dL/g) were unsuccessful due to limitations with the molding equipment.

4. Reinforcement of PLA plates with hydroxylapatite

Hydroxylapatite is a biodegradable ceramic and is present in bone. We suspected that the addition of hydroxylapatite as a filler material could provide reinforcement to polymer plates prepared by the injection-molding process.

a. Preparation of amorphous calcium phosphate (ACP)

To obtain the ceramic material, we first prepared calcium phosphate by a procedure in which solutions of calcium nitrate (pH=11.5) and 0.6M dipotassium hydrogen phosphate (pH=11.5) were mixed, boiled and filtered to produce a powdery cake (1). The dried cake that resulted was cracked into pellets and sintered at 1000 °C for one hour. SEM showed an amorphous product at 7,000X magnification.

A 50% mixture of the ACP and L-PLA (IV = 1.5 dL/g) was injection molded by the same procedure as that described above for L-PLA. The product showed a homogenous dispersion of the ACP within the polymer; however, the results of standard flexural tests showed no reinforcement by the hydroxylapatite powder. These poor results were due to the amorphous form and low aspect ratio of the hydroxylapatite prepared by this procedure. Therefore, we attempted to grow hydroxylapatite crystals from a mother liquor to reinforce PLA.

In an attempt to produce a hydroxylapatite ceramic product suitable for plate reinforcement, we incorporated ACP into a number of binders and then sintered the materials. During the sintering process, grains recrystallized to form larger grains, with coalesence occuring at intersecting grain boundaries. The grain-growth process was governed by boundary-energy considerations.

The bonding systems we employed was ACP mixed with either hydroxyethyl cellulose (HEC) and hydrochloric acid (HCL) or stearic acid. A plate of 100% ACP was also prepared under identical pressing conditions.

We sintered all samples by heating them slowly from ambient temperature to 1150 °C over a period of 5.5 hours. Thermal fracture, which occurred during the processing of all samples, prevented the fabrication of sections sufficiently large for tensile testing.

We next investigated a number of different preparations and firing schedules in an attempt to produce hydroxylapatite materials of a quality acceptable for use as reinforcing materials. The ceramics prepared by these procedures were generally of poor quality and were unacceptable as a fixation-plate reinforcement material. The principal difficulties encountered during the preparation of calcium phosphate ceramics are achievement of high strength and single-phase compositional integrity. A variety of ceramic forms of hydroxylapatite [$Ca_{10}(PO_4)_6(OH)_2$] and ß-TCP (or ß whitlockite) [$Ca_3(PO_4)_2$] had been reported in the literature. We believed that the poor quality of the ceramics produced by the previous techniques was a result of the presence of multiple phases in the final sintered product. For this reason, we turned our attention to the production of a high-strength pure ß-whitlockite ceramic. ß-Whitlockite is bioresorbable, while some ceramic forms of hydroxylapatite are not.

b. Preparation of ß-whitlockite

We prepared green states which should yield 100% of ß-whitlockite ceramics by a precipitation procedure similar to the method used for precipitation of hydroxylapatite (2).

The ß-whitlockite green cake was ground into a powder with a mortar and pestle and packed into alumina crucibles. The samples were placed in the oven and heated to 600 °C over a 0.5-hour period. The temperature was then raised quickly to 1150 °C, and the samples were sintered isothermally for 1 hour, followed by a soak at 900 °C for 4 hours.

Materials prepared in this fashion were much harder than the materials prepared by any previous procedure. Therefore, due to the encouraging results, we experimented with other pressure conditions for fabricating ceramic plates of ß-whitlockite. Sturdy plates were obtained that were hard, but could be broken by hand.

Next, we examined the use of particle size combinations.

Particle size range, µm	Percentage of total wt
<53	23.8
53-106	21.8
106-150	11.6
150-250	27.7
250-297	9.6
>297	5.5

Samples composed of ß-whitlockite particles of less than 53 µm and samples composed of 30% (by weight) of particles less then 53 µm and 70% (by weight) of particles greater than 297 µm were fired in the same fashion. The 53 µm samples underwent volume reductions of 10 to 20%, and they were soft and

sandlike. Little shrinkage was evident in the 30% 53μm samples, but they were also soft and granular after firing.

Next, we investigated the effect of grinding on the sintering characteristics of dried, filtered ß-whitlockite green cake. The ground specimen was soft and sandlike after sintering. The unground specimen, however, was quite hard and had a smooth texture. Subsequent analysis by scanning electron microscopy (SEM) showed the unground specimen to have a high packing density with few void spaces.

c. Effect of various binders and coatings on the sintering characteristics of whitlockite

Filtered, unground, dried whitlockite green cake produced hard, dense ceramics on firing. Unfortunately, such a material did not lend itself to extrusion into the fibers desired for bone-plate reinforcement. Binding agents have been used for many years to facilitate the extrusion and molding of ceramic materials, and thus, we investigated a number of polymeric materials as binding and plasticizing agents for the extrusion of whitlockite rods and fibers. As a preliminary step to fiber-production studies, we examined the influence of these various agents on the sintering process of whitlockite.

We initially investigated HEC as a binding material. The HEC in water was combined with green cake to produce pastes. The pastes were then injected into alumina rods. Replicate samples, without binder, were also fabricated. All samples were dried and sintered. Although all samples cracked after drying, no additional cracking was observed during the sintering process, and each of the samples sintered to a hard, crystalline form.

We subsequently examined a procedure in which we mixed the aqueous HEC solution with re-suspended green cake material (50%, v/v). The resulting thick white mixture was filtered until a pastelike filtrate was obtained. The paste was then extruded into rods. These rods appeared to be smoother and to contain fewer breaks than rods extruded from filtrate containing no binder. The samples were dried and sintered. A hard, brittle product was obtained.

Poly(vinyl alcohol) (PVA) and poly(ethylene oxide) (PEO) were also investigated as binders. Filtered, unground green cake and either was mixed with a small quantity of 10% PVA in water to obtain smooth pastes. Small rodlets of this material were extruding with PEO. Rodlets consisting of filtered, unground green cake containing no binder were used as controls. The rodlets were dried and sintered. Each of the samples sintered to a brittle form.

We also examined lanolin, glycerol, silicone oil, and PCL as potential binding agents. Rods fabricated using lanolin, glycerol, and silicone oil as binding agents did not hold together during drying, so these samples were not sintered. Tough elastic rods were prepared by mixing dried green cake with molten PCL and extruding. The rods were dried, sintered, heat soaked and cooled. The rods did not sinter well, and they were broken and very fragile.

The use of binders did not, in any case, produce products of acceptable quality after sintering. Because migration of binding agents may have been

responsible for crack introduction and propagation as well, we examined a number of materials as coatings for extruded whitlockite materials.

d. Dry spinning trials on ß-whitlockite

Although we were unsuccessful in producing samples with good sintering characteristics using the syringe or melt-index method, we felt that more acceptable materials might be produced using a ram extruder capable of generating high, more uniform extrusion pressures. Thus, we conducted dry-spinning trials on whitlockite with and without binder.

For paste containing no binder, the paste was charged to the extruder at room temperature, and extrusion was attempted. We were unable to extrude filaments continuously because the paste became too viscous to flow. Short monofilaments were too weak to support their own weight. The dried filaments were brittle and too fractured to be sintered.

We also attempted to extrude ß-whitlockite paste containing PEO. The trial was repeated with another sample of the same paste. No filament flow was obtained in either procedure. Dry-spinning of both pastes and pastes containing binder were unsuccessful in producing an acceptable fiber from whitlockite.

e. Evaluation of CaAl

Because dry-spinning of ß-whitlockite had proven unsuccessful, we began to examine CaAl as an alternative to whitlockite. CaAl is both bioabsorbable and biocompatible. We examined the dry-spinning and sintering characteristics of pastes made from CaAl and PEO as well as the sintering characteristics of pressed CaAl powders containing no binder.

Initially, we investigated the sintering characteristics of packed, dry CaAl powder. After a pressed sample was allowed to cool, the resulting material was soft and flaky. A duplicate sample heated through a different 1650 °F, as opposed to 800 °F used previously, was harder.

Next, we examined the sintering characteristics of CaAl containing PEO as a binder material. The resulting material was light and hard, exhibiting little chipping. Samples containing higher concentrations of binder and subjected to the same firing conditions were more fragile than samples containing less binder.

We also examined the possibility of extruding CaAl paste into fiber form by a dry-spinning process. We were able to extrude continuous rods at room temperature by this process. The rods fired. Some of the rods were removed from the oven and quickly cooled to room temperature. Another batch of extruded rods was allowed to cool slowly to room temperature inside the oven. Rods subjected to both cooling cycles were smooth and exhibited crack-free surfaces. Both sets of rods, however, were granular in cross section and could be reduced to a powder using hand pressure.

f. Preparation of fine-grained whitlockite particles by microencapsulation

Because dry-spinning of both ß-whitlockite and CaAl had proven unsuccessful, we turned our attention to the production of fine-grained whitlockite in an attempt to obtain better extrusion characteristics and greater densification on firing.

Abrasive grinding of ceramic materials, such as that encountered in ball milling, is plagued by excessive time requirements and low yield of small-particle-size fractions. Southern Research Institute has been successful in preparing small-diameter polymeric spheres by microencapsulation techniques in a number of our other research projects, and we investigated microencapsulation as a means of producing hydroxyapatite particles of a size sufficient for producing fine fibers. We attempted to prepare microspheres of hydroxyapatite using calcium nitrate and ammonium phosphate. Hydroxyapatite was precipitated into silicone oil and the resulting microspheres were coated with ethylcellulose.

The photomicrograph presented in Figure 13 shows the lack of integrity of uncoated particles after drying. The photomicrograph presented in Figure 14 shows that we were able to obtain microspheres of hydroxyapatite coated with ethyl cellulose in the 40- to 50-μm range by this procedure. From the figure it is easily seen that intact microspheres were obtained, even after drying, with the aid of ED. We extruded the coated particles into a 0.05-in.-diameter rod with a melt indexer operating at 180 °C. The rod was placed in an oven heated to 2150 °F and maintained at this temperature for 4 h. The oven was then turned off and allowed to cool slowly to room temperature. The rod did not sinter and was highly fragmented. Although microencapsulation was shown to produce small particles, the necessity of coating the particles to prevent agglomeration during drying would seem to preclude fiber formation with particles prepared by this procedure because the polymers used for coating do not have sufficient thermal stability to bind the spheres together until sintering has been initiated.

g. Preparation of ceramic fibers by wet spinning

As an alternative to dry spinning, we examined the possibility of using wet spinning to produce fibers from both ß-whitlockite and CaAl. Fiber production by wet spinning (Figure 15) involved extruding a mixture of ceramic powder, binder, and solvent into a trough or bath containing a nonsolvent for the binder. During extrusion into the nonsolvent bath, the mixture coagulates to form a fiber or filament. The fibers or filaments are subsequently drawn from the coagulating bath by using a series of water-flushed, heated godets to rinse and evaporate the remaining solvent. After passing through the rinsing and drying system, the fibers are taken up on a winding reel. The collected fibers are then soaked in distilled water to assure complete solvent removal and are thereafter dried in an air-circulating oven to produce the final dried fiber. For the production of fibers from both ß-TCP and CaAl, it is necessary to sinter the dried fibers in an inert atmosphere maintained above 1150 °C to achieve coalescence and densification of the ceramic particles.

The collected, unfired, hydroxyapatite fibers were white and more elastic than the calcium aluminate fibers because of a higher binder content. The

Figure 13. Non-coated hydroxyapatite particles after drying.

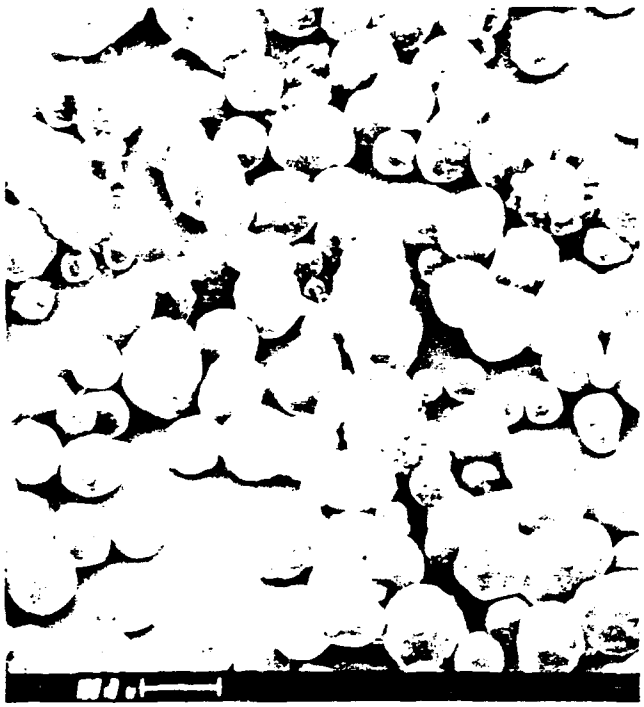


Figure 14. Hydroxyapatite particles coated with ethyl cellulose.

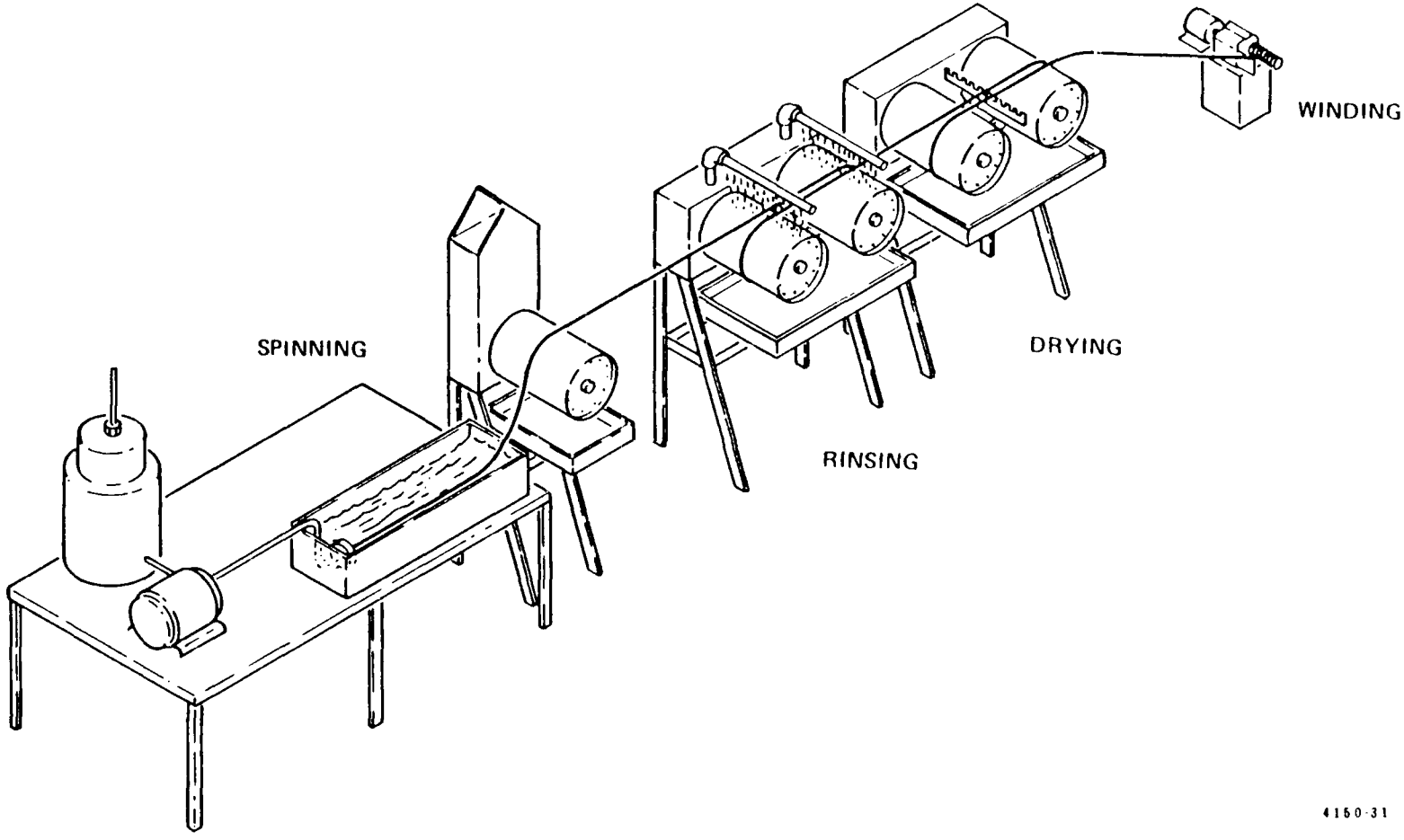


Figure 15. Schematic of wet-spinning apparatus.

collected, unfired, calcium aluminate fibers were gray initially, but turned dull-white during final drying. The calcium aluminate fibers were more brittle than the hydroxyapatite fibers because of a higher solids loading.

The fired hydroxyapatite fibers were shiny, black, and fragmented. This condition was a result of high binder content and large particle size. The fired calcium aluminate fibers were intact and white. Both types of fibers were brittle, but the CaAl fibers were more satisfactory than were the hydroxyapatite fibers.

As a consequence of the elevated temperature required for proper sintering of both of these materials, polymeric binders with superior thermal stability are required for use in the wet-spinning process. Although no polymeric resin yet produced is capable of withstanding these temperatures, we chose for examination three highly thermally stable resins which we felt might effectively bind the ceramic powders in fiber form until preliminary sintering (lower temperature) was achieved. We investigated Barex 210, a terpolymer mostly composed of acrylonitrile; PAN-Type A (PAN-A); and Ethocel #1 Standard, an ethycellulose material, as potential binders.

PAN converts from a linear polymer to a ladder network upon heating in an oxidative environment. We felt that partial conversion of the linear resin to a ladder formation would increase the thermal stability of the resin and allow us to obtain a fiber with improved sintering characteristics. Ceramic fibers were prepared using all three of the highly thermally stable resins chosen for examination.

We prepared fibers containing 60 wt % TCP and 40 wt % Barex 210 resin by wet spinning. Fibers containing 80 wt % TCP were prepared similarly. Untreated samples of the same fibers were used as controls. The pretreated fibers appeared after firing. Although there were no obvious differences in fragility of samples pretreated for various times, the pretreated samples were in each case less fragile and more easily handled than the control fibers. Samples with the higher ceramic content were somewhat stronger than samples containing a lower ceramic loading.

We repeated the experiment using 250 °C as the oxidative pretreatment temperature. Samples subjected to treatment at this temperature and then sintered under the previously described conditions were weaker than samples that had been treated at 200 °C. Similar results were found when PAN-A was substituted for Barex 210 as a binding material. There was, however, no obvious improvement in sintering characteristics as a result of using the acrylonitrile homopolymer.

Samples of fibers with 80:20 ethanol/toluene solvent and surfactant-deionized water coagulation bath were formed by using syringes and needles. In this coagulation bath, the fibers floated to the top, resulting in fibers flat in cross section rather than round. The fibers were dried, sintered at 1200 °C for 1 h under a nitrogen purge, and tested for breaking strength. Figure 16, an SEM photograph of one of these fibers taken at the fracture surface, shows the flattened cross section. The breaking strength of these fibers prepared with the ethylcellulose binder was less than 300 psi. Because these fibers were inferior to those with PAN-A as a binder, we abandoned any further work with ethycellulose as a binding material.

Figure 16. Scanning electron micrograph of the fracture surface of sintered tricalcium phosphate fiber made with ethylcellulose binder.

As a further portion of our work on ß-TCP, we examined the influence of fiber diameter on the tensile strength of filaments produced from this material. Spinning dope was prepared using dimethylsulfoxide (DMSO) as the solvent, PAN-A as the binder, and wet sieved TCP powder. After pretreatment the fibers were sintered and became light yellow. After sintering, some of the fibers shrank to less than 40% of their original diameter.

The fibers were then tested for breaking strength. The fibers were prepared for testing by mounting on cardboard tabs. The finest fibers were attached to the tabs with paraffin, and the larger fibers were attached with sealing wax. After being tested, the samples were removed from the breaking machine, and the diameter at the fracture point was determined with a micrometer. The fracture surfaces were then examined by SEM. The test results are presented in Table XXI. There is a dramatic effect of fiber diameter on tensile strength. As fiber diameter decreases, the strength increases. Such behavior is commonly found in the preparation of ceramic fibers. Results shown in Table XXI reflect the average of test results for five specimens of each fiber diameter. One sample of the smallest-diameter fiber had a tensile strength of 2500 psi. SEM photos showed voids and irregularities at the fracture surface of all specimens. In general, larger voids were associated with lower breaking strength.

In an attempt to make a denser TCP fiber with fewer voids and thus increase its strength, we investigated the possibility of preparing a coaxial fiber comprised of a pure TCP core enclosed by a PAN-A sheath. These sintered fibers were discontinuous and misshapen. Apparently, the sintering caused stress to the PAN-A sheath, which broke the fibers. Figure 17 shows an end view of one of the sintered coaxial fibers. The fibers appeared denser than fibers prepared with previous techniques, but there were many fissures in the fibers. None of these fibers had enough integrity to allow evaluation of tensile strength.

Because we found that the breaking strength of the TCP fibers was inversely proportional to the fiber diameter, we investigated making finer fibers to see if we could further increase the breaking strength.

For the first pilot-plant run, a dope consisting only of the PAN-A binder and DMSO solvent was used so that the best conditions for making fibers with this polymer could be determined. After this run, the ceramic-loaded dope was used. The dope consisted of 10% TCP, 2.5% PAN-A, and 87.5% DMSO. Fibers produced from this trial were sintered to give fibers 0.05 mm in diameter, but the average breaking strength of the fiber was less than 100 psi.

Fibers of CaAl were prepared following the procedures used for ß-TCP fiber production and using the same solvent and binder. After sintering, the fibers were so fragile that they could not be removed from the oven without breaking.

Because we were unable to produce ceramic fibers of sufficient integrity and strength, we then chose to evaluate other alternatives toward the fabrication of bone plates.

TABLE XXI. BREAKING STRENGTH OF TRICALCIUM PHOSPHATE FIBERS

Average diameter, mm	Breaking strength, psi
0.559	169
0.508	353
0.356	69
0.124	419
0.122	477
0.074	1607

4150-30

Figure 17. Scanning electron micrograph of the end view of a sintered coaxial tricalcium phosphate fiber with polyacrylonitrile sheath.

5. Cross-linking of biodegradable polymers

The lack of success in preparing ceramic fibers with high tensile strength and modulus prompted us to examine cross-linkable biodegradable resins as an alternative means of achieving initially strong and rigid fixation plates.

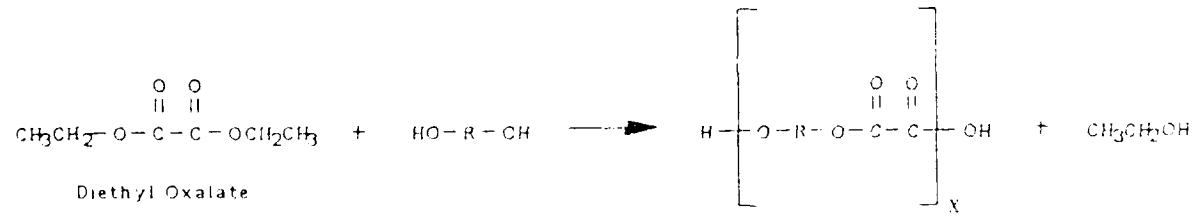
a. DL-PLA

As an alternative to composite fabrication, we examined crosslinking of PLA as a method of enhancing stiffness and rigidity. In general, polymeric materials with moderately high flexural strengths and moduli may be obtained by chemical crosslinking of polymer chains. Crosslinking reduces polymer mobility by covalently bonding subunits of different polymer chains. Decreasing chain mobility reduces the extent to which a material may relieve imposed stresses by deformation and in many cases alters the failure mechanism from plastic yield and deformation to brittle fracture at high load levels. In addition to the desired increase in load at failure, it is also necessary with crosslinked polylactide used as bone plates that the crosslink bonds be subject to biodegradation to harmless end products. With this in mind, we investigated several methods of crosslinking PLA.

The results of all of our experiments with PLA indicated that the introduction of crosslinking moieties into the polymer chain would be difficult, and we diverted our efforts to biodegradable polymers prepared by a different polymerization mechanism.

b. Copolyoxalates

The lack of success in crosslinking DL-PLA prompted us to examine other biodegradable resins as possible boneplate materials. Isomorphic copolyoxalates had been patented (U.S. Patent 4,141,087) as synthetic absorbable suture materials. The polymerization of the copolyoxalates proceeds by a transesterification reaction and was hoped to be used for the incorporation of a trifunctional, crosslinking molecule than does the ring-opening polymerization of polylactide. Highly crystalline isomorphic polyoxalate polymers may be prepared as shown below by reacting mixtures of cyclic and linear diols with dialkyl oxalate, preferably in the presence of an inorganic or organometallic catalyst.



Diethyl Oxalate

Where: R = $-(CH_2)_6-$ [1,6-hexanediol]

or $-CH_2-C_6H_{10}-CH_2-$ [1,4-cyclohexanedimethanol]

For our initial studies with these materials, we prepared 95/5 poly(trans-1,4-cyclohexylenedicarbinyl-co-hexamethylene oxalate). Although the final product was insoluble in chloroform, it was suspected that the insolubility was a result of crystallinity and high molecular weight and was not a result of crosslinked polymer. Therefore, further attempts to crosslink this biodegradable polymer were abandoned.

6. Examination of biodegradable glasses for fiber production

Due to the relative lack of success in producing TCP, ß-TCP, and phosphate-free CaAl fibers with mechanical properties adequate for fixation-plate reinforcement, we investigated absorbable glasses as an alternative to ceramic materials for biodegradable-fiber production. These glasses exhibit good interfacial bonding with natural bone as a result of the exchange, at the interface, of the cations between the bone and the glass.

a. Bioglass fibers

As a preliminary step in this program, we investigated the fiber-forming properties of Bioglass, a partially biodegradable glass composed of ≈45% silicon dioxide. Fibers prepared by drawing molten Bioglass (≈900 °C) varied considerably in both fiber diameter from sample to sample and in uniformity of diameter throughout the length of a given sample, as evidenced by the large variation in breaking strength (9,000 psi to 50,000 psi). Figure 18 shows a longitudinal view of a typical Bioglass fiber. Breaking strengths were determined by the method used for the ceramic fibers.

b. CMP

The formation of Bioglass fibers with high tensile strengths was most encouraging. Therefore, our next attempts were directed toward obtaining high tensile strength, uniform fibers from alternative, easily processed, totally biodegradable glass. For this reason, we evaluated CMP as a potential fiber-forming compound.

i. CMP salt precursor

It was originally believed that fibers could not be produced from commercially obtained CMP due to impurities in the CMP. Therefore, high-purity CMP was prepared by the method described in U.S. Patent No. 4,049,779, "Crystalline salt monomers for stable phosphate glasses." In this method, phosphoric acid solution was reacted with $CaCO_3$ to produce calcium metaphosphate. Impurities were removed by precipitation with ammonium 1-pyrrolidine dithiocarbamate solution and filtration. CMP-salt prepared in this manner had a trace metal impurity content of 100 to 200 ppm, and melted at 1000 °C.

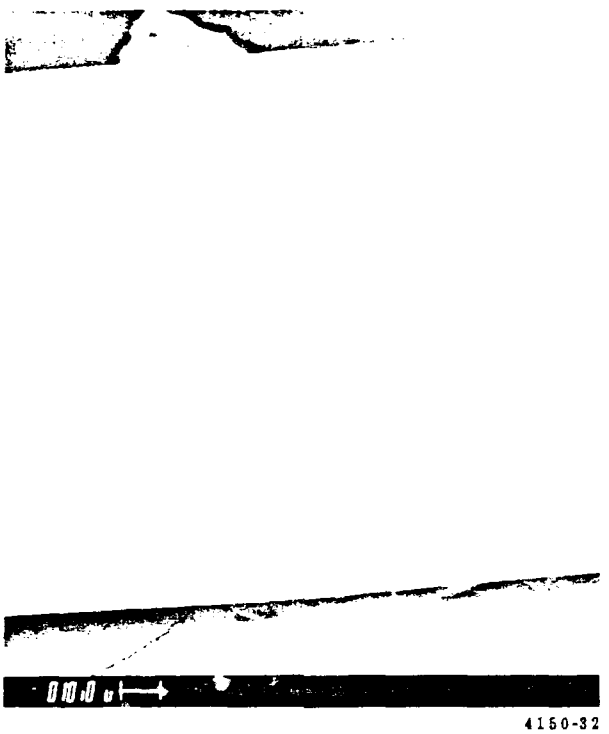


Figure 18. Scanning electron micrograph of a bioglass fiber.

2. Drawing of fibers

To prepare fibers from the CMP, the salt must first be polymerized. This is accomplished by placing the salt in an alumina-oxide tray and heating it in a furnace at 600 °C for 24 h and then at 800 °C for 48 h. The resulting soft-greyish ash was transferred to an alumina-oxide crucible and heated to its melting temperature. The crucible was then removed from the furnace and heated with a torch to prevent the glass from cooling too rapidly. Once the glass had cooled to the desired viscosity, CMP fiber was drawn from the surface of the melt. To facilitate in the production of continuous lengths of CMP fiber, a take-up winder was constructed.

3. Determination of CMP-fiber properties

In vitro studies were performed to determine the degradation rate of the CMP fibers. Thirty-two fiber samples, 2 to 3 cm in length, were placed in 0.9% USP saline. Degradation was assessed by visual inspection of the fibers. There was a definite visible difference in the appearance of the fibers after 10 days, and after 20 days all of the fiber samples had completely dissolved.

Tests were also performed to determine the tensile strengths of the hand-drawn CMP fibers. The crosshead speed was set at 1 in. per minute. Tensile strengths of the fibers generally varied between 12,000 and 51,000 psi, with one CMP fiber specimen exceeding 110,000 psi. The variation in tensile strengths was primarily due to variations in sample diameters, with the smaller samples having higher tensile strengths.

4. CMP-reinforced, biodegradable composites

Due to the encouraging results of the biodegradable fibers obtained from the CMP, we then attempted to incorporated the fibers into biodegradable composites with DL-PLA as the composite matrix.

a. Composite Preparation

Initially, we attempted to fabricate our biodegradable composites by solution-coating unidirectionally oriented CMP fibers with DL-PLA. After coating and drying both surfaces of the resulting film, the polymer/fiber film was pressed and redried to remove residual solvent. The CMP-fiber-reinforced films wer then laminated with nonreinforced DL-PLA films, resulting in a composite plate with uniformly oriented fibers.

As an alternative to heat lamination, DL-PLA/CMP composites were also fabricated using solvent lamination. In this process, spun cast films were dried, and cut into 3- x 0.5-in. lengths. CMP fibers were placed on the DL-PLA film and brushed with dichloromethane. This process was repeated for a total of six laminating layers, resulting in a composite comprised of seven film layers and six CMP fiber layers. The final pressed composite proved to be the more suitable appliance.

b. Composite evaluation

Solvent-laminated composite samples fabricated as described above were subjected to mechanical tests to determine the flexural moduli and maximum

midspan stress by the method used for the determination of the flexural properties of the nonreinforced polymer plates. Tests were conducted in accordance with the three-point bending test outlined by the ASTM D790 Standard Test Method for Flexural Properties of Plastics and Electrical Insulating Materials. For this test method, the composite beam is supported by two points, 2 in. apart. The active load is applied at the midspan. The maximum stress calculated in the outer fibers at the midspan was 6.6×10^3 psi. The flexural modulus of elasticity was determined to be 1×10^6 psi, approximately half that of bone.

5. Improvement in CMP fiber quality

After experiencing difficulty drawing smooth, continuous fiber with subsequent batches of CMP, we began examining methods for improving the quality of the CMP.

a. Higher-purity CMP salt precursor

Fresh salt precursor, prepared due to suspicions that the CMP glass had begun to degrade or had become contaminated, failed to produce fiber from the melt. To ensure that the CMP glass we were preparing in our laboratory was of sufficient purity for fiber formation, we prepared additional salt precursor following the second method outlined in the U.S. Patent No. 4,049,779. The precursor was prepared as described earlier except that the $CaCO_3$ was added after filtering, whereupon the remaining purification steps were repeated for a second time. This alternate method reportedly reduces the impurities of the glass from 100-200 to 10-20 ppm. No differences were noted in the fiber-drawing capabilities of the higher-purity CMP prepared using this method and the CMP prepared by our standard method. Samples of each batch of salt precursor were given for SEM evaluation. Results showed that the composition of each sample was identical within the ranges of this technique.

b. High-alumina-content crucibles

Another possible factor inhibiting fiber formation was suspected to be the melting temperature of the crucibles. Because of the high temperatures involved, and because of the length of exposure time and the severe environment, crucible degradation was a possibility Bubbling of the crucible surface, and a hard film noted on the surface of the melt, led us to believe that the crucibles were degrading and contaminating the CMP glass, and, thus, inhibiting fiber formation. Therefore, high-alumina-content (99.6%) crucibles with a melting temperature rated in excess of 1500 °C were obtained. These high-alumina-content crucibles withstood the temperatures involved in the glass fiber production.

c. Temperature parameters

A third problem concerning CMP fiber formation was related to the polymerization temperature of the glass. For fibers to be readily drawn from a CMP melt, the glass must be sufficiently polymerized. This was achieved by baking the crystals at 600 °C for 24 h and then 1050 °C for 17 to 24 h. Fibers were readily drawn from the melt polymerized in this fashion. When the melt became too viscous to produce fibers, it was reheated in the box furnace at 1050 °C. After equilibrating for 2 h, fibers could be drawn from the

reheated melt. This procedure was repeated until the CMP was depleted from the crucible.

d. Variable drawing speed

In order to produce uniform, small diameter, high tensile fibers, the take-up rate of the fiber drawn from the melt was modified. With the process described previously for producing CMP fibers, when the melt cooled, the melt viscosity was increased, and the fiber diameter increased correspondingly when taken up at a constant rate. This phenomenon was accelerated locally on the melt surface as a vertex is formed at the point when the draw was exposed directly to the air interface. By varying the take-up rate, through visual inspection of this vertex, we controlled fiber diameter, and ultimately the tensile strength of the fibers.

e. Degradation of CMP fibers

CMP fiber was incubated in phosphate-buffered saline at 37 °C to determine the in vitro degradation rate. The pH of the saline solutions was adjusted to 6.0, 6.7, and 7.4 to determine the effect of pH on the degradation rate. Samples of fibers were removed from the bath after incubation times of one, two, three, and four weeks.

The average loss in physical dimensions for each pH range is shown in Figure 19. The pH of the saline solution apparently affected the degradation rate of the fibers, showing an increase in degradation rate with increasing pH. After four weeks of incubation, the CMP fibers exposed to the saline with a pH of 7.4 lost an average of 90% of their original mass (Figure 19B). Control CMP fibers exposed in air to the same temperature conditions as the test fibers showed no changes in dimension as seen in the SEM presented in Figure 20.

f. Tensile strength of CMP fibers

After the changes in physical dimensions of the CMP fibers had been determined, the changes in physical properties were evaluated. The tensile strength and modulus of CMP fibers were determined using an Instron Model TMS. The span length was approximately 5 cm, and the crosshead speed was 5 cm/min.

The tensile strength of CMP fibers varied greatly with fiber diameter, with the fibers of smaller diameter having greater tensile strengths. This same trend held true even after incubation in saline. Because of the nonlinear relation between CMP fiber diameter (or cross-sectional area) and corresponding tensile strength, a simple averaging of data would be misleading when presenting these results. We chose, therefore, to match each set of tensile test data with a best-fit-curve. The corresponding tensile strength for the average fiber diameter under a given condition was then read directly from these curves. The fiber diameter losses shown in Figure 19A were subtracted from the initial overall CMP fiber diameter of 140 μm and selected as the point on the best fit curves from which the tensile strengths were read. The relatively high initial fiber diameter of 140 μm was chosen so that the time duration of the study could be extended to weeks instead of days and so that all test fibers were initially of similar size.

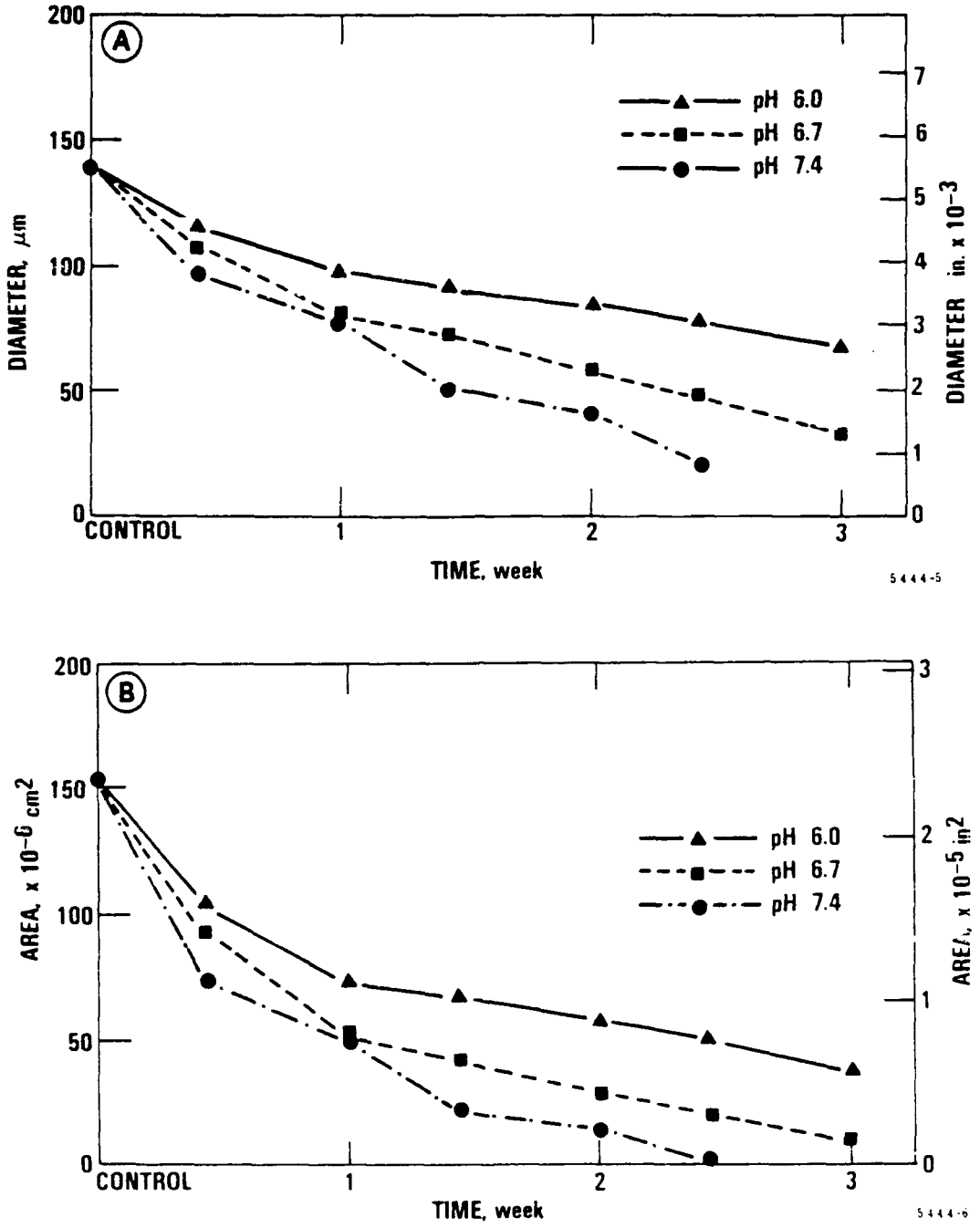
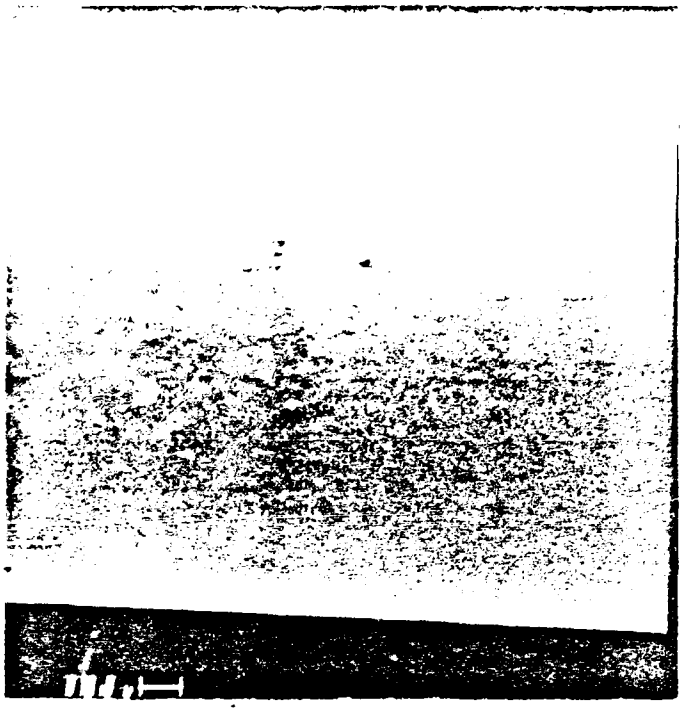
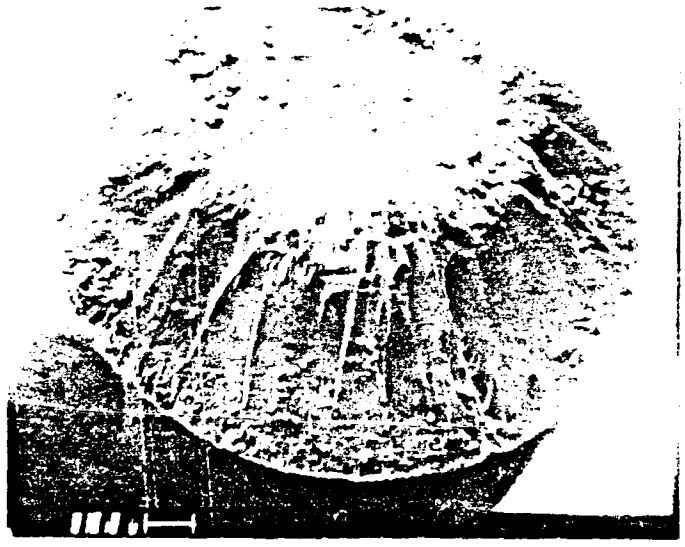


Figure 19. Change in CMP fiber dimensions as a result of incubation in saline at 37 °C (A; Diameter; B: Area).



NO. C468-138-36 [CONTROL (AIR); THREE WEEKS] SIDE VIEW



NO. C468-138-36 [CONTROL (AIR); THREE WEEKS]

5444-2

Figure 20. Scanning electron micrograph of a control CMP glass fiber exposed to air for three weeks. Top--side view; bottom--end view.

We have previously found that CMP fibers with diameters well below 100 μm have tensile strengths exceeding 7 x 10^3 kg/cm^2 (100 x 10^3 psi), while fibers with diameters in the 200 μm range fail below 1.4 x 10^3 kg/cm^2 (20 x 10^3 psi). Control CMP fibers with a diameter of 186 μm had a tensile strength of about 1.1 x 110^3 kg/cm^2 (16 x 10^3 psi). Incubation in saline resulted in a gradual decline in the force necessary to break the CMP fibers, as illustrated in Figure 21A. This trend, however, did not hold true when the tensile stress required to cause failure was calculated. As the incubation time increased, and thus the CMP fiber diameter decreased, the tensile strength of the fibers continually increased, as shown in Figure 21B. After three weeks in saline, fiber tensile strength increased to over three times that of control fibers.

This phenomenon is probably a result of the erosion of micro flaws on or near the fiber surface caused by differential cooling during the fiber forming process. Figure 19A indicates that CMP fiber degradation is primarily caused by surface erosion, as the curves show a linear relationship with time. The erosion process is also evidenced by the scanning electron micrographs of Figures 20 and 22 comparing the roughened surface of a CMP fiber after three weeks in saline to a smooth surface of a fiber exposed only to air. As the erosion process occurs, an increasing number of these micro flaws are eliminated, leaving the higher quality core of the fiber with relatively fewer flaws.

6. Preparation of biodegradable laminated composites

In addition to optimizing our CMP fiber-drawing capabilities, we also examined ways to improve our composite fabrication techniques. We had previously found that a combined solvent/heat-lamination technique provided us with the best composites. This method of composite fabrication involved alternating layers of DL-PLA polymer and CMP glass fibers.

a. Film preparation

The DL-PLA films were prepared by injecting a 5% solution of DL-PLA in dichloromethane into rotating, 4-in. spin cups. The solvent was allowed to evaporate between injections. The dried films were then removed from the spin cups and cut into 0.5 x 3-in. sections.

b. Composite fabrication

Composite fabrication was initiated by placing a 0.5 x 3-in. polymer film into the mold. This mold consisted of three plates of tooled steel. The mold plate has a 0.5 x 3-in. rectangular cavity which was bolted to a solid base plate. The top plate was tooled so that it could fit snugly into the mold plate, leaving a 0.125-in. clearance. After the first polymer film was placed into position, a preweighed amount of 3-in.-long CMP fibers was placed longitudinally on the film. A small amount of a dilute DL-PLA/dichloromethane solution was then brushed onto the fibers to aid in bonding the fibers to the polymer films. Another polymer film was then placed on top of the fibers, and the procedure was repeated for a total of eight film layers and seven glass-fiber layers. The top plate was then put into place, and the entire mold was then placed into a heated vacuum chamber for several hours to remove the solvent.

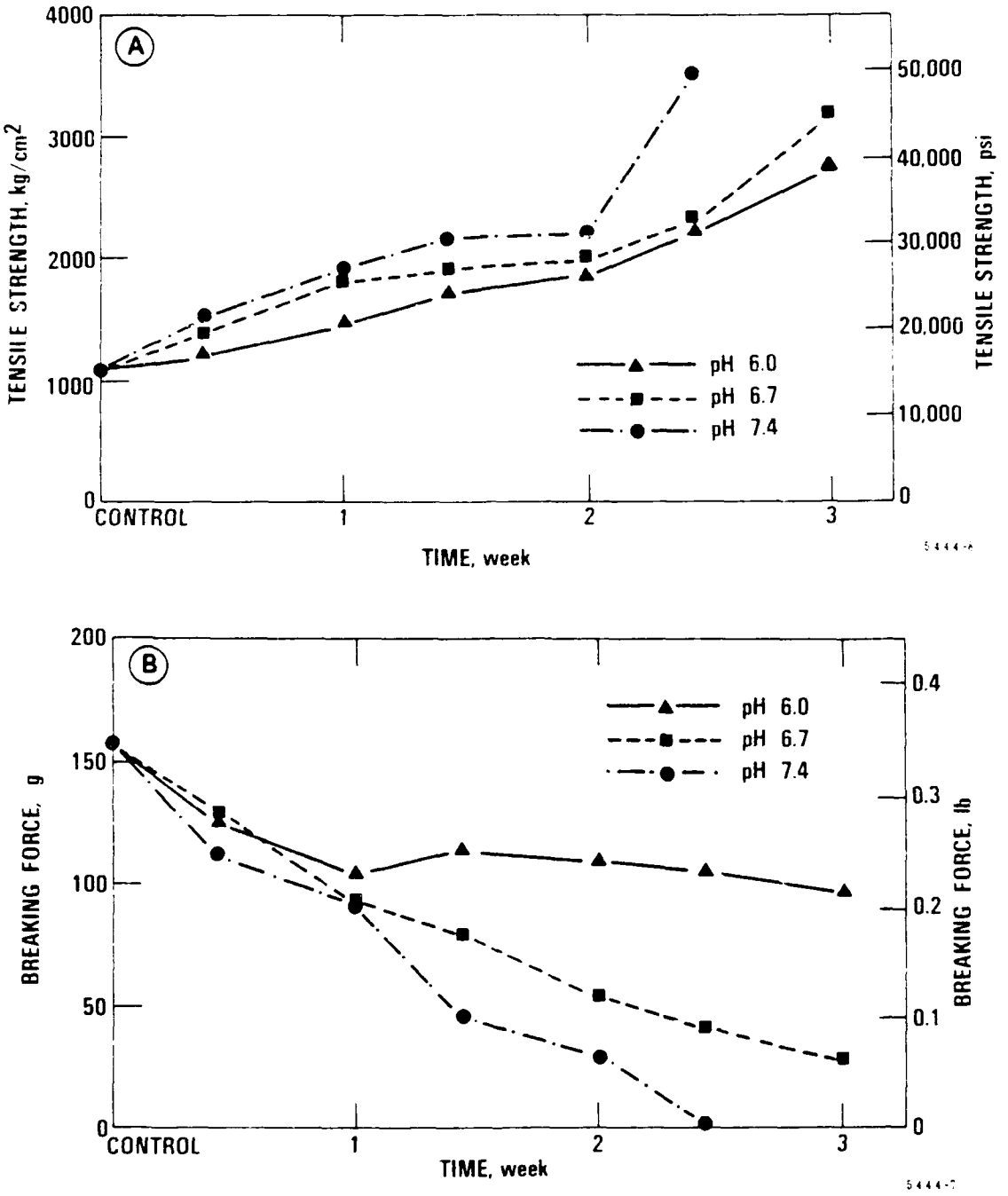


Figure 21. Change in mechanical properties of CMP fiber after incubation in saline at 37 °C (A: Tensile Strength; B: Breaking Force).

NO. C468-138-19 [pH = 6.7; THREE WEEKS]

NO. C468-142-20 [pH = 6.7; FOUR WEEKS] 54444

Figure 22. Scanning electron micrograph of a CMP glass fiber bathed in phosphate-buffered saline (pH 6.7) for three weeks (top) and four weeks (bottom).

Upon removal from the vacuum chamber, the mold was placed in a heated hydraulic press. After the mold reached thermal equilibrium, it was slowly pressed until the top plate became flush with the mold plate. Excess polymer was removed from the composite through the escape ports. The composite sample was then removed from the cooled mold cavity.

Twenty-five CMP-reinforced plates fabricated using these procedures were supplied to USAIDR for evaluation in canines under the direction of LTC Eric S. Koppelman.

e. Composite evaluation

CMP-reinforced composites using DL-PLA as the matrix material were mechanically tested to determine their flexural strength and modulus. Tests were conducted according to the procedures outlined in the ASTM D-790. The flexural modulus of these DL-PLA composites averaged 2.3 x 1^0_6 psi (15 x 10^9 Pa) while the average flexural strength was calculated to be 29 x 10^3 psi (200 x 10^6 Pa). These values are well within our targeted values of 1 to 3 x 10^6 psi (6.9 to 2.1 x 10^9 Pa) for the flexural modulus and 10 to 20 x 10^3 psi (69 to 140 x 10^6 Pa) for the flexural strength.

7. Scale-Up of CMP Fiber-Drawing Procedures

The CMP fibers prepared thus far had been hand drawn from the top surface of a CMP melt. The salt precursor necessary for the melt was also prepared in our laboratory. Before the salt precursor could be converted into a homogeneous and polymerized melt, it had to be heat-treated as described previously. All of these procedures were time consuming, and although we had a great deal of success drawing high-quality CMP fibers, extremely labor-intensive efforts were required before quantities of fibers required for testing and evaluation were produced. Therefore, we established a method for producing CMP fibers on a more time- and cost efficient basis.

Our first efforts were to provide a more time- and cost-effective method, were to obtain monobasic CMP from a commercial source and discontinue the time consuming laboratory production of CMP glass precursor. When exposed to the same prebaking procedures as the glass precursor prepared in our laboratory, the commercial CMP formed a homogeneous melt from which fibers were easily drawn. The polymerization time using this precursor, 7 h at 600 °C and 17 h at 1050 °C, was much shorter than that used with the laboratory batches of CMP.

Our second modification was to develop a technique of producing uniform fibers more efficiently. This technique involved drawing fiber from the bottom of the melt, as industry does when preparing glass fibers for insulation, reinforcing, and optics. To accomplish this, a two-zone, split-tube furnace was designed. The core of the tube furnace allowed for the placement of two crucibles aligned along a vertical axis. Each crucible was positioned in one of the two independently controlled heating zones. The upper crucible melted the polymerized CMP, which then dripped through a small orifice in the bottom of this crucible to the lower (drawing) crucible. The drawing crucible also contained a small orifice in its bottom from which CMP fibers were drawn and then collected on a motorized, take-up winder located beneath the furnace.

Although this apparatus was a marked improvement over the past drawing-apparatus, problems relating to stability, contamination, and temperature control were still encountered. These problems were then eliminated by the installation of a specially designed fiber-drawing apparatus (Figures 23-26).

The primary problem associated with the fiber-drawing system was the collection of semimolten CMP on the bottom of the drawing crucible originating from the crucible orifice. This was largely eliminated by modifying the crucible (Figure 23). The redesigned crucible contained a small nipple in the center of the crucible's floor through which an orifice was drilled. Molten CMP continuously flowed through the orifice because the nipple prevented migration of the molten glass.

To prevent contamination of the CMP from extraneous sources, the holding crucible was fitted with a crucible lid as shown in Figure 24. A handle was provided such that it could easily be removed with tongs when CMP beads were added.

A chimney effect was created as air was drawn up through the furnace due to furnace design. To alleviate this condition, a special top plate was designed as shown in Figure 25 to eliminate the flow of air through the furnace. The plate was designed so that the crucible support cage (Figure 26) would still be accessible for positioning the crucibles within the center of each heating zone of the furnace. The cage was constructed from high-purity alumina to prevent possible contamination from lengthy exposure to high temperatures.

The crucible support cage was controlled by a motorized drive shaft. This system allowed the operator to position each crucible to the desired height in the furnace without contacting any of the heated surfaces. This system also facilitated superior temperature control because the crucibles could be repositioned in fine increments within the furnace.

To prepare glass fiber, beads of CMP were first prepared by pouring the molten glass onto Inconel 601 alloy plates and allowing the glass to cool to room temperature. The beads were then placed in the holding crucible and lowered to the upper heating zones of the split-tube furnace. (approximately 1080 °C). Once the CMP was molten (approximately 20 min), it began to drip into the lower extrusion crucible (1000 °C). The extruding crucible was then lowered, and the fiber exiting the drawing orifice was collected on the take-up winder.

Samples of these fibers were tested to determine their mechanical strength. The fibers were glued to cardboard tabs prior to testing to aid in handling and gripping. The average diameter of fibers produced from the 2-mm-orifice crucible was about 30 μm, which gave a tensile strength of 58,000 psi. Previously drawn CMP fibers had an average tensile strength of 18,000 psi and an average diameter of about 140 μm.

As expected, these smaller diameter CMP fibers had a much higher tensile strength than those larger fibers prepared using our old drawing system. This diameter-to-strength relation is depicted in Figure 27 where we have plotted the tensile strength of CMP fibers as a function of their diameter. Although we realize there is considerable scatter of the data, we believe the true

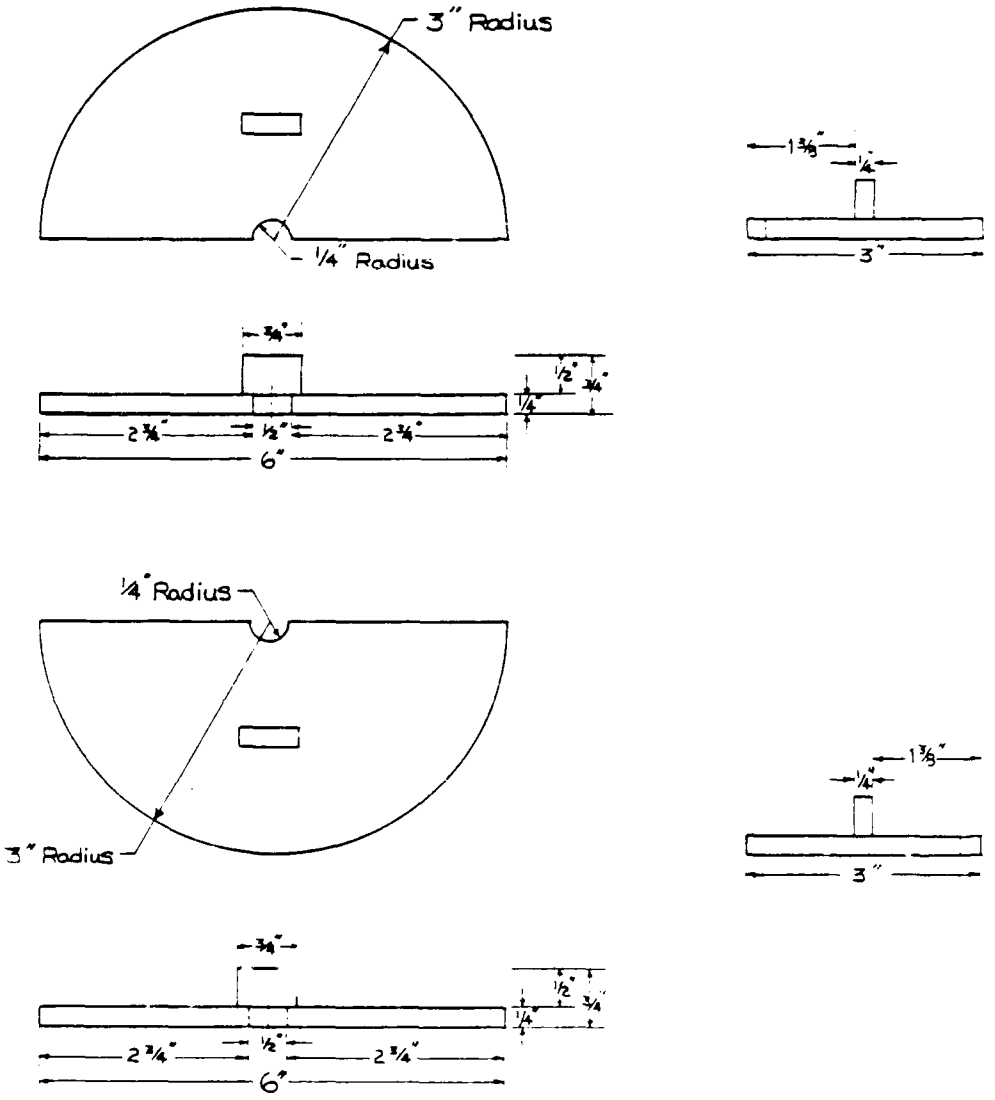


Figure 23. Furnace top plate halves (Scale: 1/2 in. = 1 in.; Material: alumina, 99.7% Al_2O_3).

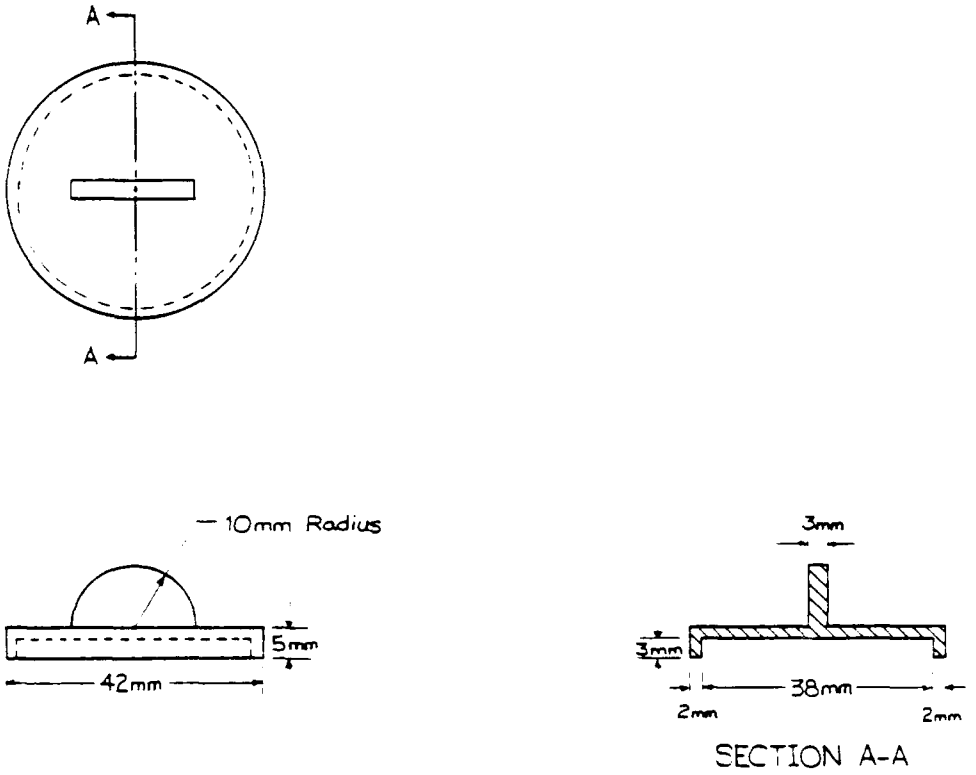


Figure 24. Crucible lid (Scale: 1 mm = 1 mm; Material: alumina, 99.7% Al_2O_3).

NOTE: If possible, we would like the hole drilled through the crucible nipple to be tapered, with the diameter of the hole at the base of the crucible = 2 mm, and the diameter of the hole at the end of the nipple = 1 mm. The taper of the outer diameter for the crucible nipple is determined by your necessary wall thickness for drilling.

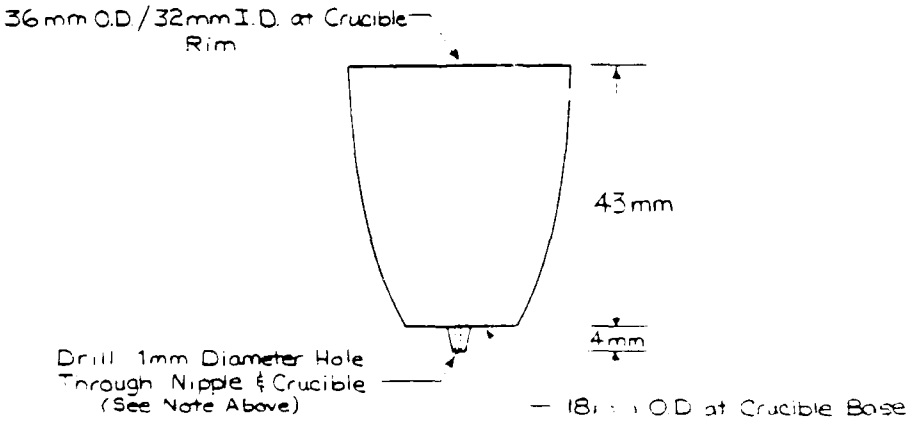


Figure 25. Crucible (capacity 20 ml) (Scale: 1 mm = 1 mm; Material: alumina, 99.7 Al_2O_3).

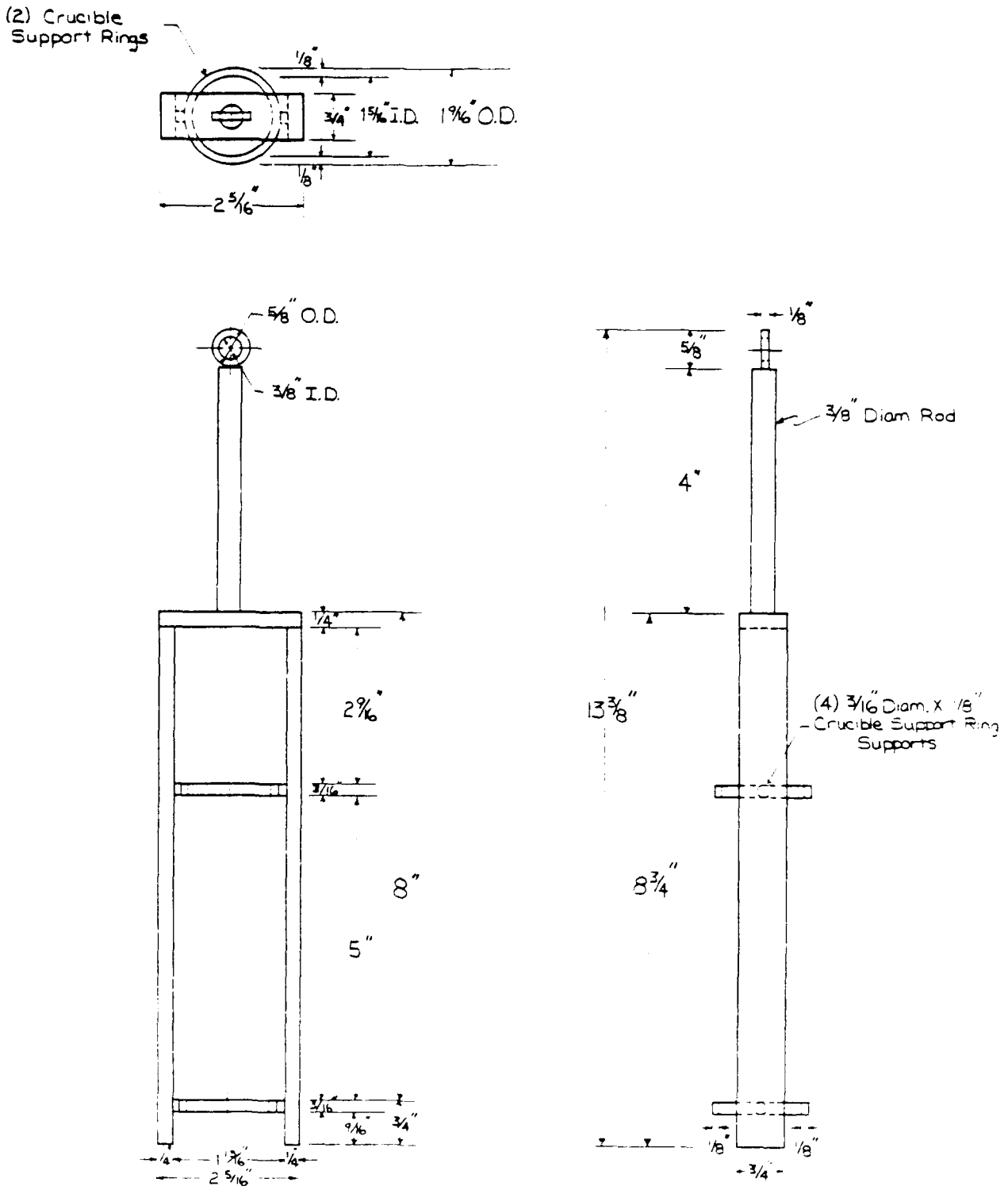


Figure 26. Crucible support cage (Scale: 1.2 in = 1 in.; Material: alumina, 99.7% Al_2O_3).

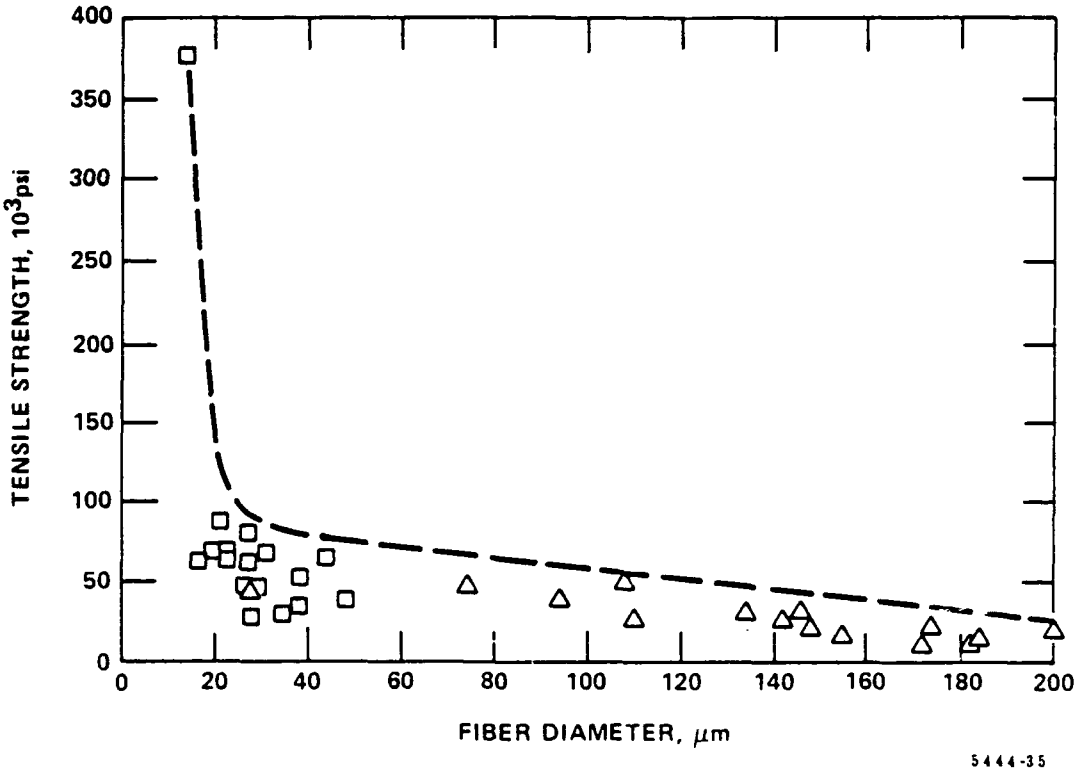


Figure 27. Tensile strength as a function of fiber diameter for calcium metaphosphate fibers drawn either by hand (△) or from the split-tube furnace (□).

tensile strength is greater than that bounded by the dashed line. This line represents the upper limit of the collected data. Because we are unable to perform true tensile tests on brittle glass fibers--i.e., no misalignment, bending, or crushing--all generated data are less than the true or actual tensile strength. The dashed line in Figure 27 shows a strong correlation between CMP-fiber diameter and tensile strength. This is typical of glass fibers, primarily due to relatively fewer imperfections on the surface of the smaller fibers. Composite plates were then fabricated from these smaller fibers to determine their effects upon composite properties.

Because of the success of the 2-zone fiber drawing system, several improvements to glass fiber production were implemented. These included 1) the increase in the diameter of the fiber take-up reel from 2.5 to 6.5 in. to produce smaller diameter, higher-strength fiber, and 2) the use of a platinum instead of an alumina crucible from which the fiber is drawn. The larger take-up reel permits drawing at roughly 2.5 times previous rates. The platinum crucible appears to permit superior heat conduction from the furnace to the melt, thus allowing continuous drawing of glass fiber for longer than two hours. The limiting factor for the duration of figer-drawing was the lack of continuous feeding of polymerized glass beads into the upper melting crucible.

8. Optimization of Composite Fabrication

To determine if incorporation of these higher quality fibers increased the overall composite strength and modulus, we then prepared DL-PLA/CMP composite plates. Previously plates were prepared using a lamination technique whereby CMP fibers were solution coated with DL-PLA. This technique greatly aided in the surrounding of the fibers by the polymer matrix. Because of the relatively large distances the solvent had to diffuse, it could not be completely removed from the polymer matrix using our drying techniques. This remaining solvent acted as a plasticizer and compromised the plates' ability to resist forces, particularly torsional forces. We were also concerned about the effects of residual solvent on the biocompatibility and toxicity of plates used as implants. For these reasons, we modified our composite fabrication technique to exclude the use of solvent. Instead of spin casting the films of the biodegradable polymer, the films were heat-pressed to their dried thickness and then were cut into 3 x 0.5-in. rectangles for use in composite fabrication.

Because solvent was eliminated from our fabrication process, we decreased the quantity of fiber per lamination layer to aid in the impregnation of the fibers by the polymer. Therefore, these composites were comprised of 14 layers of CMP instead of the seven used in previous plates. The volume of fiber per plate remained at 65% of the total plate volume. To ensure that all of the fibers were completely surrounded by polymer, the polymer films were essentially of the same thickness.

Composites were fabricated by alternating layers of DL-PLA films and CMP fiber in the heated base of a three-piece compression mold. A new mold was tooled to compensate for the increased thickness of the unpressed composite, which resulted from the additional volume of polymer. The mold was then slowly closed between the heated platens of a hydraulic press. To allow the excess polymer to exit the mold during the closing procedure, escape ports

were incorporated into the design of the molds. The resulting composite plate was removed from the cooled mold.

In our evaluations, we used both a high and a medium molecular weight DL-PLA (IVs = 2.44 and 0.96 dL/g). The processing conditions were varied to provide the strongest possible composites while maintaining the integrity of the polymer. The results of these evaluations are illustrated in Figures 28 and 29. From these graphs, it can be seen that the strongest and toughest plates are those processed for 21 to 40 min at 175 °C for the 0.96 dL/g DL-PLA. Evaluation of the 2.4 dL/g DL-PLA showed that the optimum processing conditions were inconclusive, but it appears that higher temperatures are required for these plates. These results are illustrated in Figures 30 and 31.

Improper processing conditions result in void spaces around the fibers, as illustrated by the scanning electron micrograph of the cross section of a composite plate prepared at 110 °C (Figure 32). The rough outer surface of the composite and the variations in fiber diameter can also be seen. Figure 32 shows a similar view of a composite pressed at 150 °C. The polymer appears to more completely surround each reinforcing fiber with fewer void regions. Again the wide distribution in fiber diameter can be seen.

Plates fabricated using this technique had a flexural modulus and strength of up to 2.2×10^6 psi and 30×10^3 psi. These values compare favorably to DL-PLA/CMP composite plates fabricated using the solvent/heat-laminating technique and supplied to the USAIDR for implantation into canines.

9. Composite evaluation in vitro

To assess ways to reduce the rapid strength loss of the resorbable composite, we chose to incubate the composite plates at 37 °C in physiologic saline to mimic the environment in vivo. After incubation in the saline for various periods, the plates were removed from the bath and tested in three-point bending. Because of the large amount of time and materials required to fabricate each composite, we decided to cut each of our standard 0.5 x 3 x 0.125-in plates into four equal pieces before incubating. The resulting composites thus had dimensions of approximately 0.234 x 1.5 x 0.125 in. Because of the relatively short length of these composites, it was necessary to decrease the support span of our three-point-bending apparatus from 2 to 1.25-in.

After these plates were cut and then placed in saline, they lost the majority of their mechanical strength after only one day. It was believed that the rapid decrease in strength was due to fluids wicking along the fiber/matrix interface. It was also believed that fluid was wicking along the spaces between CMP fibers that were not completely surrounded by the DL-PLA matrix. Because the CMP fiber ends were exposed after the samples were cut, these ends were in direct contact with the saline. Typically, the fiber ends are somewhat protected and isolated, although this mechanism of degradation probably played an important role in our initial studies in vitro using the same types of plates that were used in USAIDR's animal studies. Because drill holes were used to accommodate the metallic fixation screws, we believed that

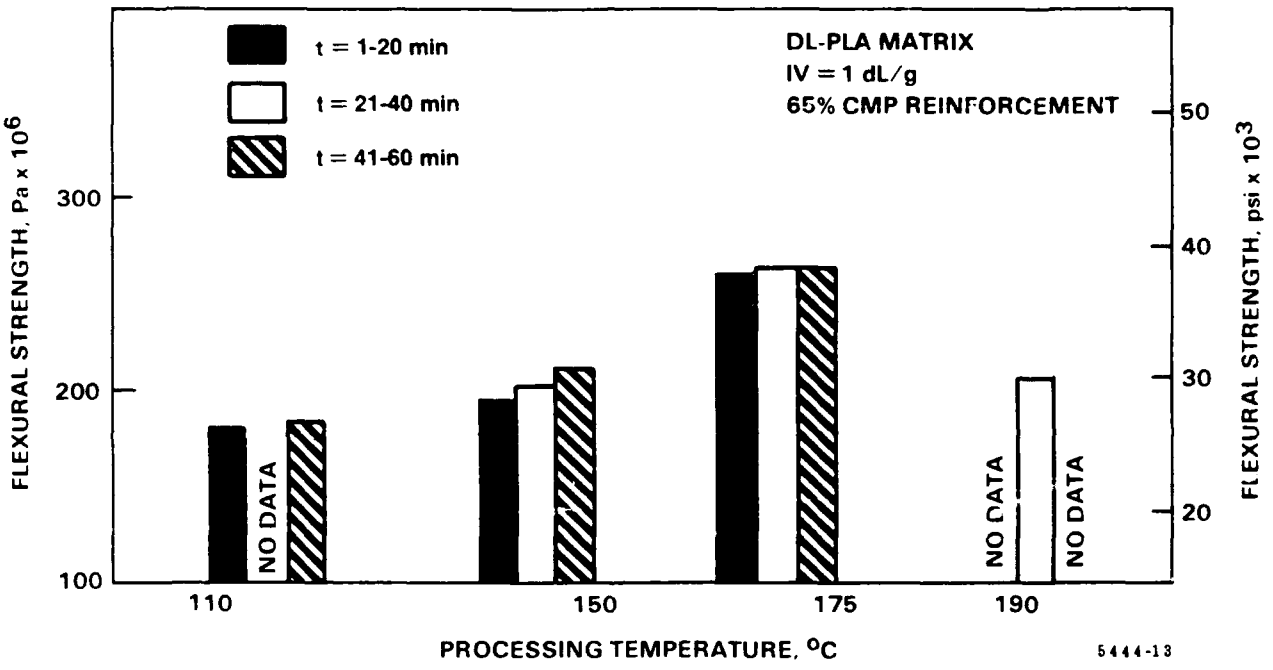


Figure 28. Effect of processing temperature and molding time on flexural strength of DL-PLA (IV = 0.96 dL/g)/CMP composites.

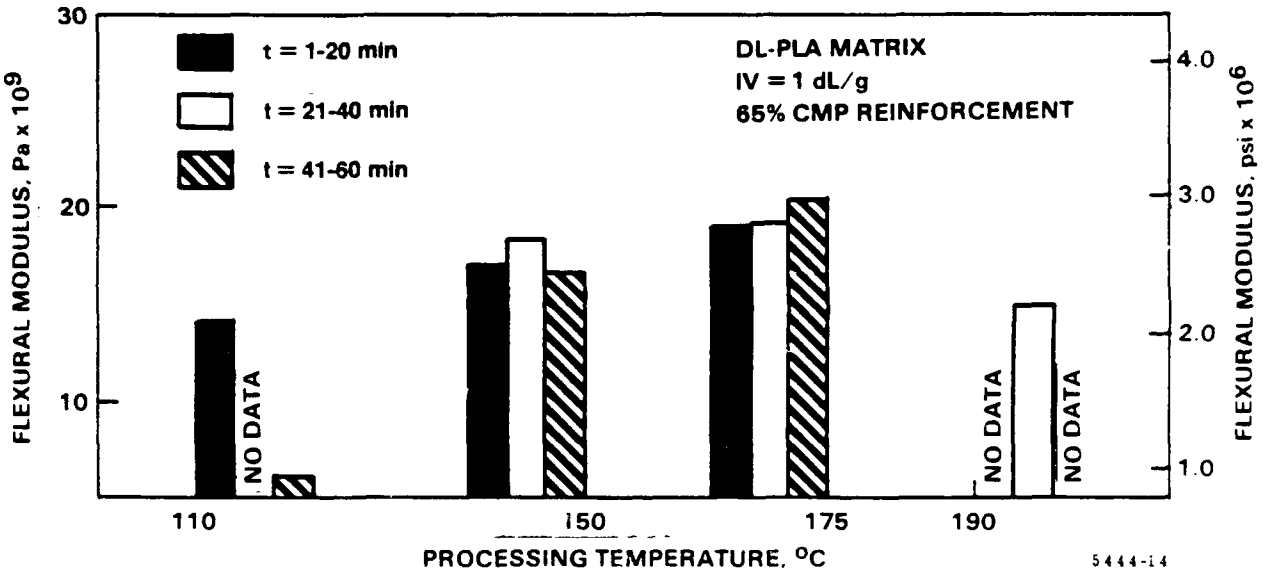


Figure 29. Effect of processing temperature and molding time on flexural modulus of DL-PLA (IV = 0.96 dL/g)/CMP composites.

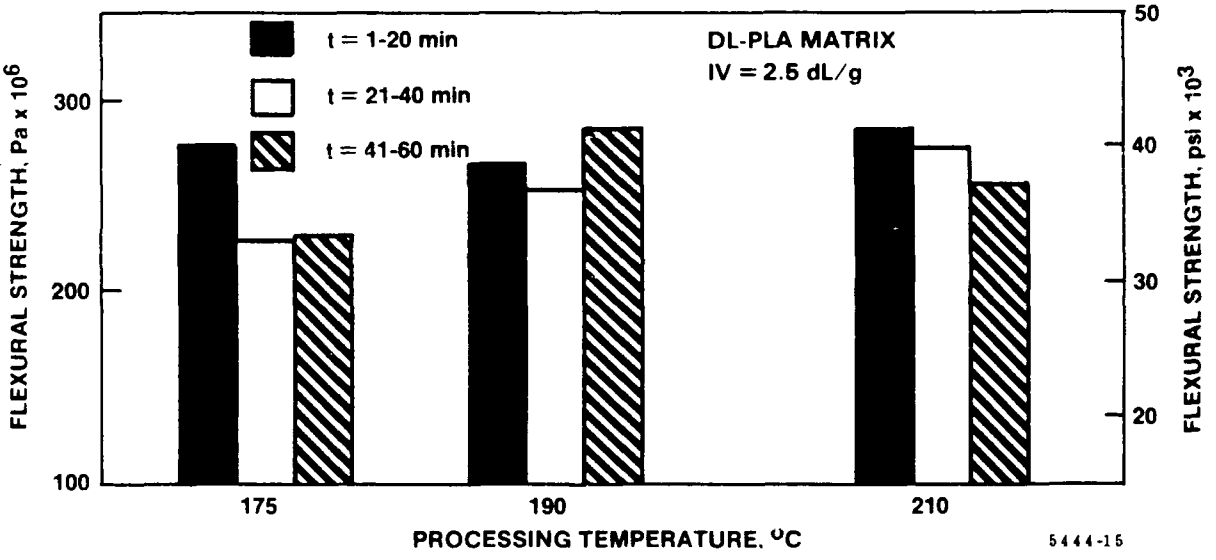


Figure 30. Effect of processing temperature and molding time on flexural strength of DL-PLA (IV = 2.44 dL/g)/CMP composites.

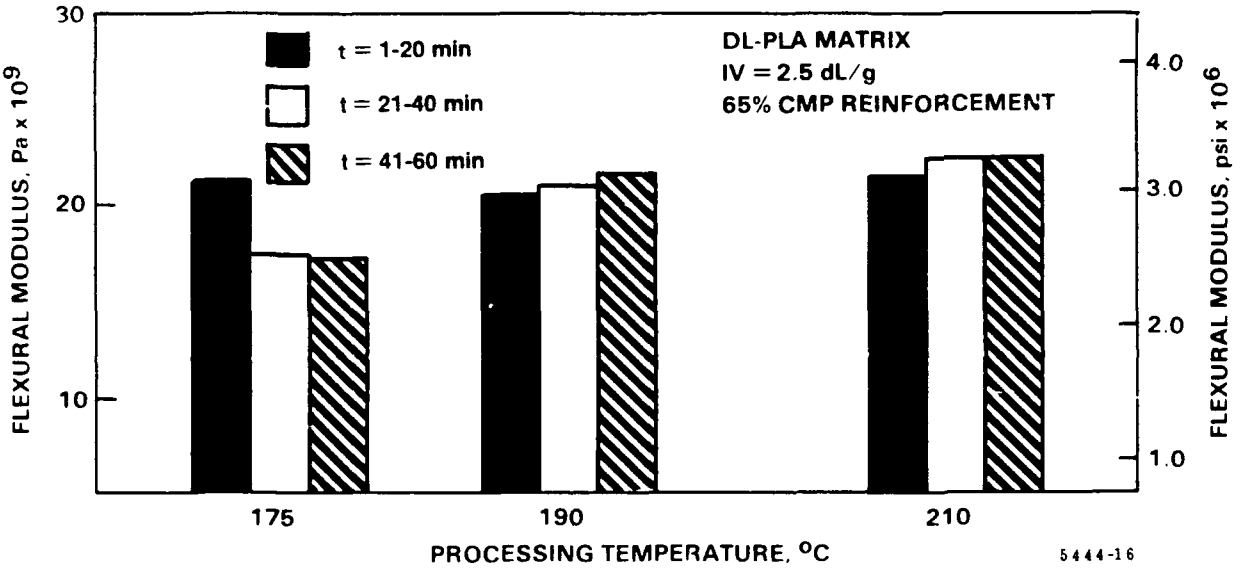


Figure 31. Effect of processing temperature and molding time on flexural modulus of DL-PLA (IV = 2.44 dL/g)/CMP composites.

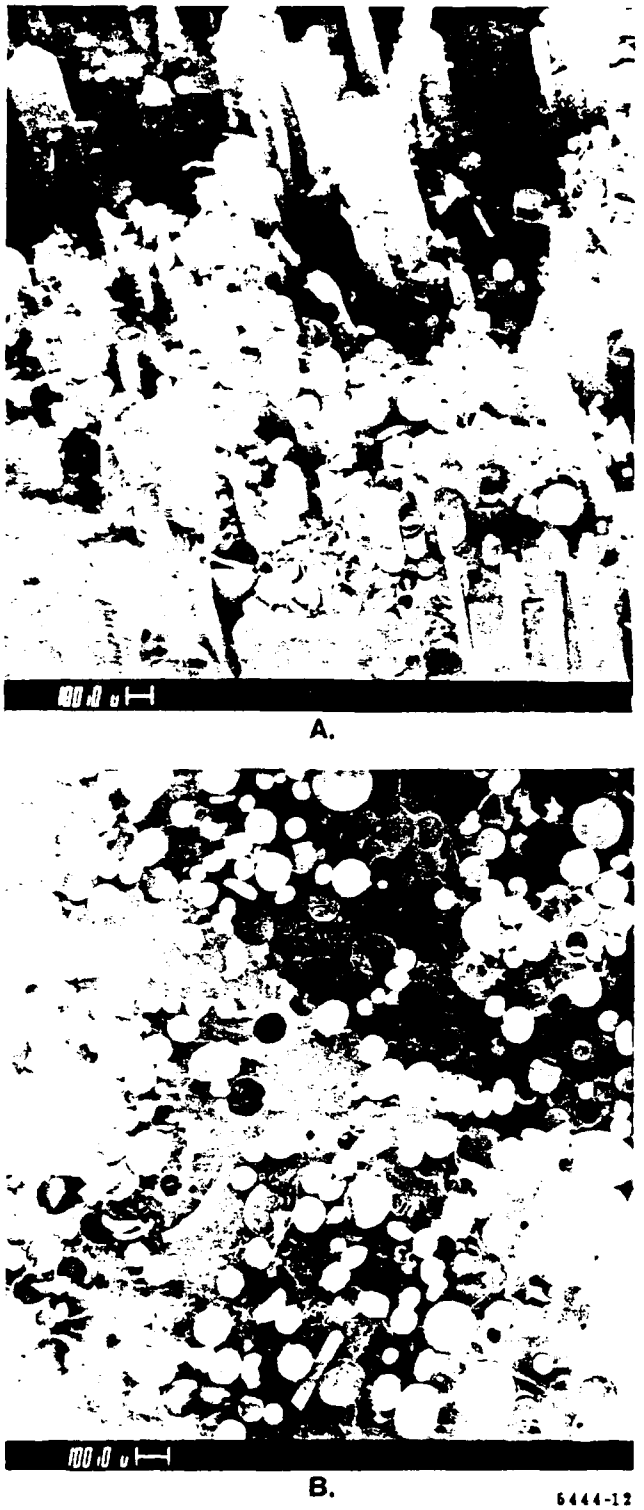


Figure 32. Scanning electron micrographs of the cross section of a DL-PLA/CMP composite plate pressed at: A. 110 °C and B. 150 °C.

this type of mechanism may have been predominant in the rapid loss of mechanical properties seen by USAIDR.

10. Effects of volume-fraction loading on physical properties of CMP-reinforced composites prepared from small-diameter CMP fibers

The rapid decline in flexural properties observed for cut or drilled plates in vitro and in vivo led us to examine possible explanations for and prevention against this rapid loss. Because we had previously shown voids to exist at the polymer/fiber interface, it was possible for fluids to enter the composite along these voids, thus destroying the polymer/fiber interface and decreasing composite strength. To reduce the void spaces and improve the polymer/fiber interface, we prepared composites reinforced with small-diameter CMP fibers produced on our split tube furnace. Because these small fibers are stronger than previous hand-drawn fiber, it was possible to reduce the fiber-volume loading, providing less available space for wicking, while maintaining the strength of the plates. The following studies were conducted using solventless techniques to determine the effects of fiber-loading on the flexural properties of the plates.

Initially, plates were prepared with 65% by volume glass fiber for comparison with the 65%-loaded solvent plates. Table XXII and Figure 33 compare the weakening of full-size and mini composite plates after being incubated in saline at 37 °C. The flexural properties were determined by testing the composites in 3-point bending. In contrast to earlier studies, there was not a catastrophic failure of the plates after being incubated in saline for 1 day, although the reduction in strength and modulus was substantial. Also in contrast to previously reported results, the differences in the response between the full-size plates and the cut mini plates was not substantially different. Because these plates were made using identical fabrication procedures and fiber-volume fractions used previously, this increased stability when exposed to saline was believed to be due solely to the use of the smaller-diameter CMP fibers. Although fiber ends of the mini plates were directly exposed to the saline, the pores or orifices created between adjacent CMP fibers were small enough to limit the rate at which the saline could enter the composite, and thus effect the polymer/fiber interface.

Having shown that reducing fiber diameter improves composite performance in vitro, plates were then prepared to determine if a reduction of the CMP fiber loading would further improve the properties in vitro. Plates loaded with 65, 50, and 35% by volume small-diameter CMP glass fibers were prepared and evaluated for strength retention in vitro. Table XXIII and Figure 34 depict the changes in flexural properties of these plates after incubation in saline at 37 °C. The composite plates containing 35% by volume CMP retained a greater portion of their initial strength and modulus than did the 65%-by-volume plates. Because a large difference in initial properties was not observed, the plates containing 35% CMP fibers were stronger and stiffer than similar plates containing 65% CMP fibers. These data suggested that reducing the CMP fiber concentration from 65 to 35%, results in a further reduction of space available for wicking fluids. This is to be expected since the DL-PLA has a greater access to the surface of each reinforcing fiber. Also, because the polymer matrix serves to transfer the stresses between reinforcing fibers, the increased coverage results in a better stress transfer between fibers and the

TABLE XXII. COMPARISON OF THE LOSS OF FLEXURAL PROPERTIES OF 65% BY VOLUME CMP-REINFORCED[a] DL-PLA COMPOSITES AFTER INCUBATION IN PHOSPHATE-BUFFERED SALINE AS A FUNCTION OF TIME

Composite	Flexural modulus, psi (10^6), after incubation for			Flexural strength, psi (10^3), after incbation for		
	0 days	1 day	7 days	0 days	1 day	7 days
Full Size	1.22	0.88	0.28	45.2	27.6	11.8
Mini	1.46	1.02	0.18	35.4	21.6	8.0

[a]Small-diameter fibers.

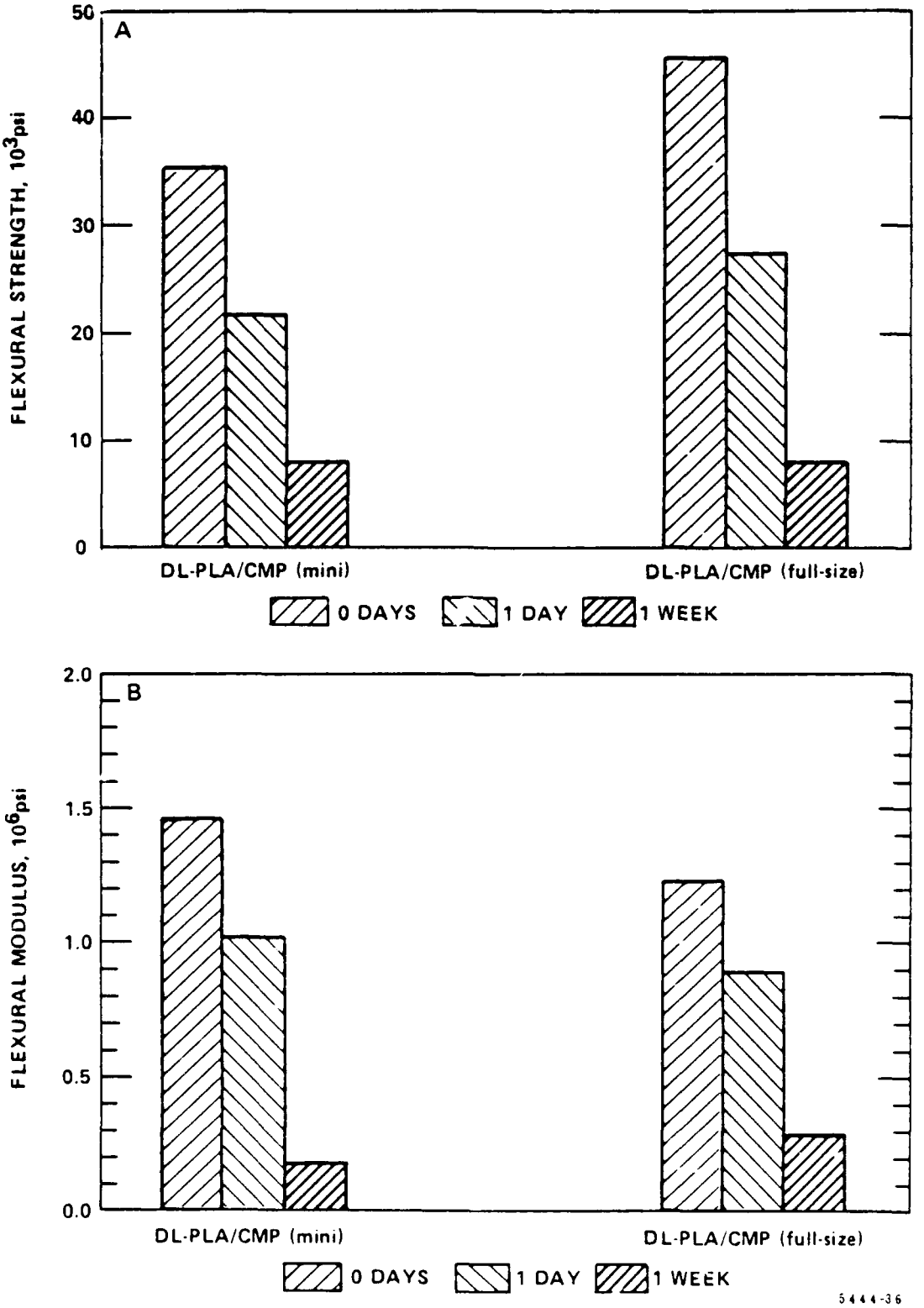


Figure 33. Change in flexural properties of full-size and mini compsite plates reinforced with 65% by volume small-diameter CMP fibers after incubation in phosphate-buffered saline as a function of time: A) flexural strength, and B) flexural modulus.

TABLE XXIII. LOSS OF FLEXURAL PROPERTIES OF CMP-REINFORCED[a] DL-PLA MINI COMPOSITES AS A FUNCTION OF INCUBATION TIME IN PHOSPHATE-BUFFERED SALINE

CMP fiber volume, %	Flexural modulus, psi (10^6), after incubation for			Flexural strength, psi (10^3), after incubation for		
	0 days	1 day	7 days	0 days	1 day	7 days
65	1.46	1.02	0.18	35.4	21.6	08.0
50	1.32	0.88	0.19	33.9	23.1	07.9
35	1.26	0.80	0.28	30.3	20.4	10.0

[a]Small-diameter fibers.

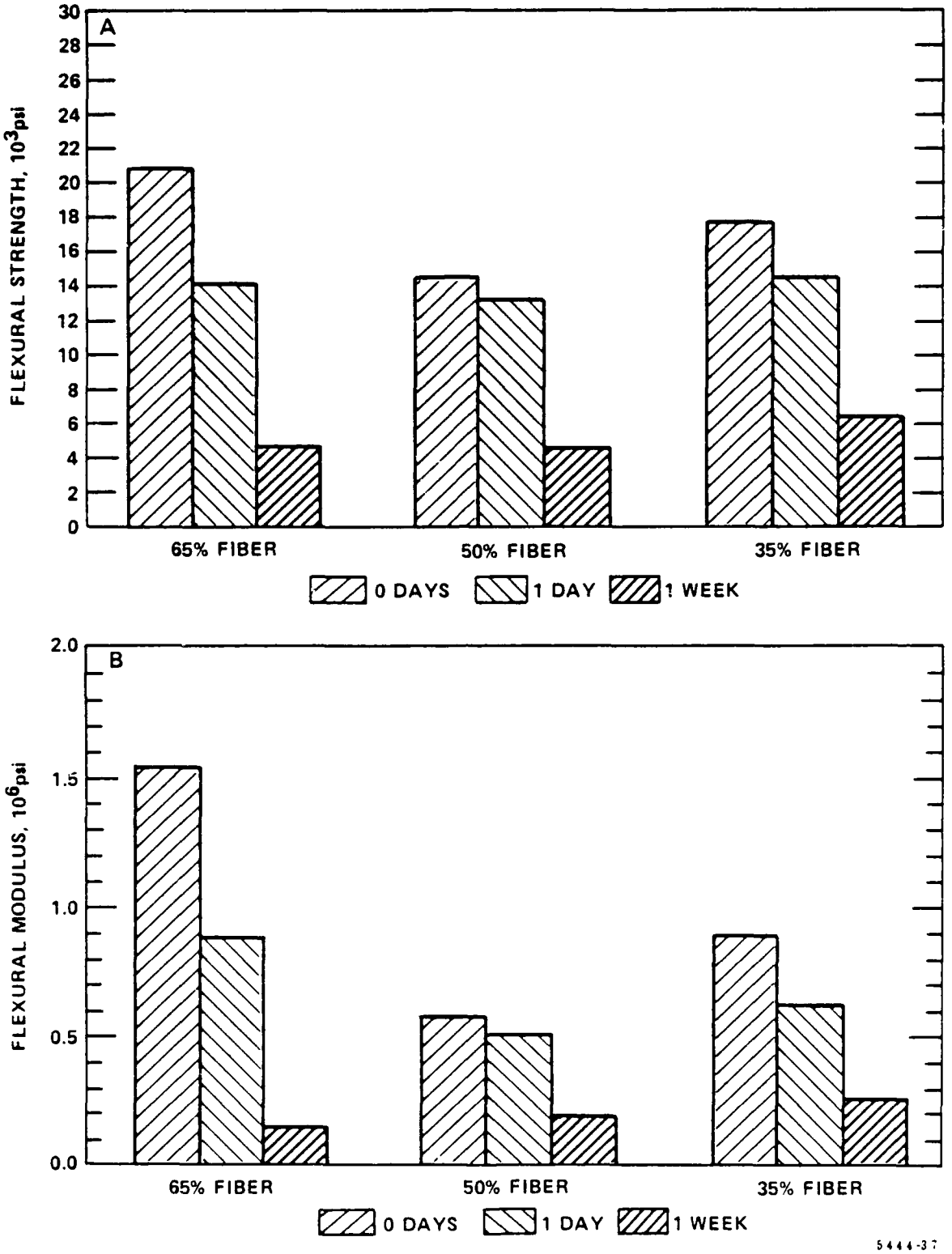


Figure 34. Effects of volume fraction of fiber on flexural properties of DL-PLA mini plates reinforced with small-diameter CMP fibers after incubation in phosphate-buffered saline as a function of time: A) flexural strength, and B) flexural modulus.

strength and stiffness of the low-volume fraction remains high. It was the combination of these two benefits, less space for fluid wicking and better stress transfer, that was responsible for retaining the composite properties after exposure to saline in vito.

11. Coating of composite to reduce wicking action

In the previous experiments, we examined ways to reduce the influx of fluid into the composite by reducing the diameter and the quantity of fiber incorporated into the composite. We also examined a method of coating the composites with a polymer coating to prevent the influx of fluid. Initially, solutions of both DL-PLA and PCL were used to coat the plates. The DL-PLA-coated samples were found to lose their mechanical strength as fast as the uncoated samples. The PCL-coated samples were found to be more resistant to water infiltration as seen by their slower loss of mechanical properties, although the loss was still significant. Because we believed that these coatings were not watertight due to holes left from the evaporating solvent, a hot-melt-coated sample was prepared by pressing a film of PCL and heat sealing this coating around the composite. Microscopic examination of the coating did not reveal any air pockets or pathways for water travel.

The results of our mechanical testing of these composite plates are shown in Figures 35 and 36. The solid lines represent the loss of mechanical properties of full-size composite plates we prepared using the same techniques as those used to prepare the plates used by USAIDR in the animal study. These are referred to as the Army solvent plates and are used as a reference. The long dashed lines represent cut mini composite plates that we prepared using heat only and are referred to as the solventless mini-plates. These plates therefore had CMP fiber ends exposed and were tested using the smaller span width. The strength and modulus of the solventless plates before they were cut is shown by the diamond on the abscissa in the figures. Large solventless plates were not evaluated in saline as described above. The short dashed lines represent mini-plates that were dip coated in DL-PLA. The dotted lines represent the mini-plates that were brush coated with PCL. The dash/dotted lines represent mini-plates that were heat sealed with a PCL film.

These figures show that all of the composite samples we tested lost at least 50% of their mechanical strength within one week. Because of the difficulty in visualizing this rapid strength loss over short time periods, these data are also plotted logarithmically in Figure 37. Dip coating the plates in DL-PLA did not slow down the rate of mechanical-strength loss and resulted in initially weaker plates. Brushing a solution of PCL onto the plates, however, did decrease the rate of strength loss, although these plates lost 75% of their strength within four weeks. The most successful coating was the heat-sealed film of PCL. These plates retained over 30% of their initial strength after being incubated in saline for one week. Even more encouraging was the retention of flexural modulus of composite plates coated with a film of PCL (Figure 38). After one week in saline, these plates had lost less than 9% of their initial modulus.

These studies indicate that a coating of PCL can reduce the rapid weakening of resorbable composites. But even more protection is required to protect the polymer/glass interface and prevent moisture from easily wicking into the composite, resulting in the destruction of this interface.

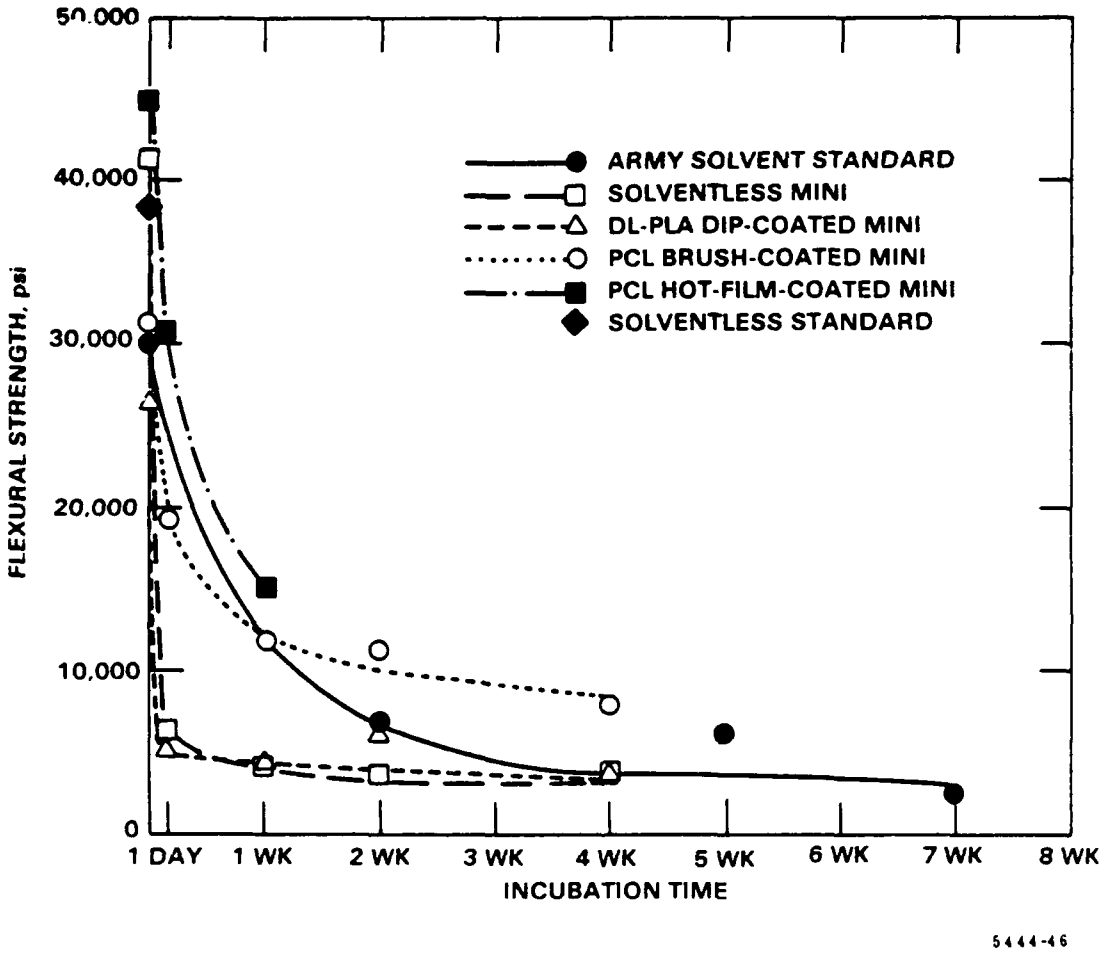


Figure 35. Flexural strength loss of various formulations of DL-PLA/CMP composites after incubation in saline at 37 °C.

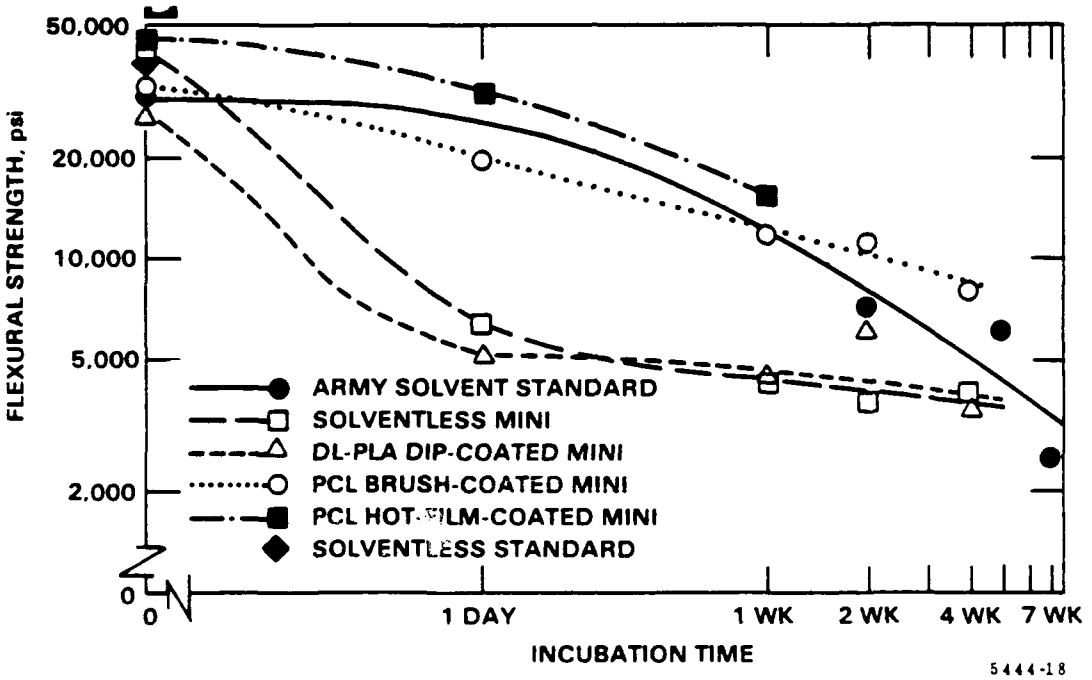


Figure 36. Logarithmic plot of flexural strength loss of various formulations of DL-PLA/CMP composites after incubation in saline at 37 °C.

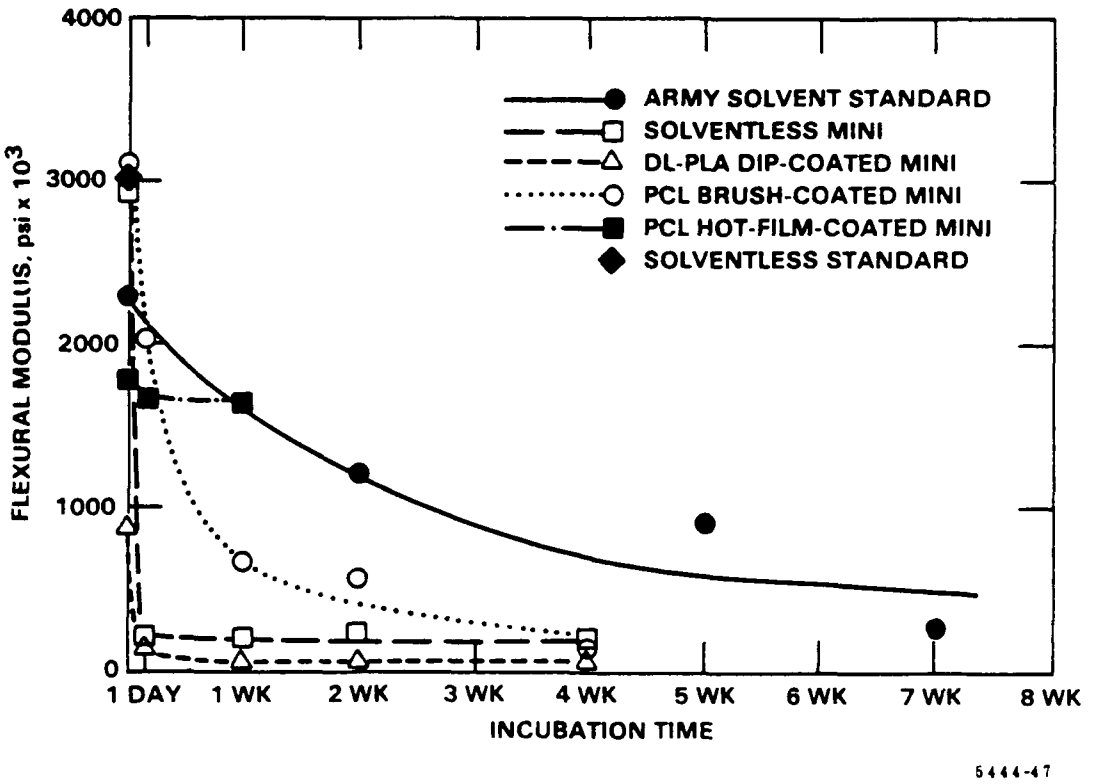


Figure 37. Flexural modulus loss of various formulations of DL-PLA/CMP composites after incubation in saline at 37 °C.

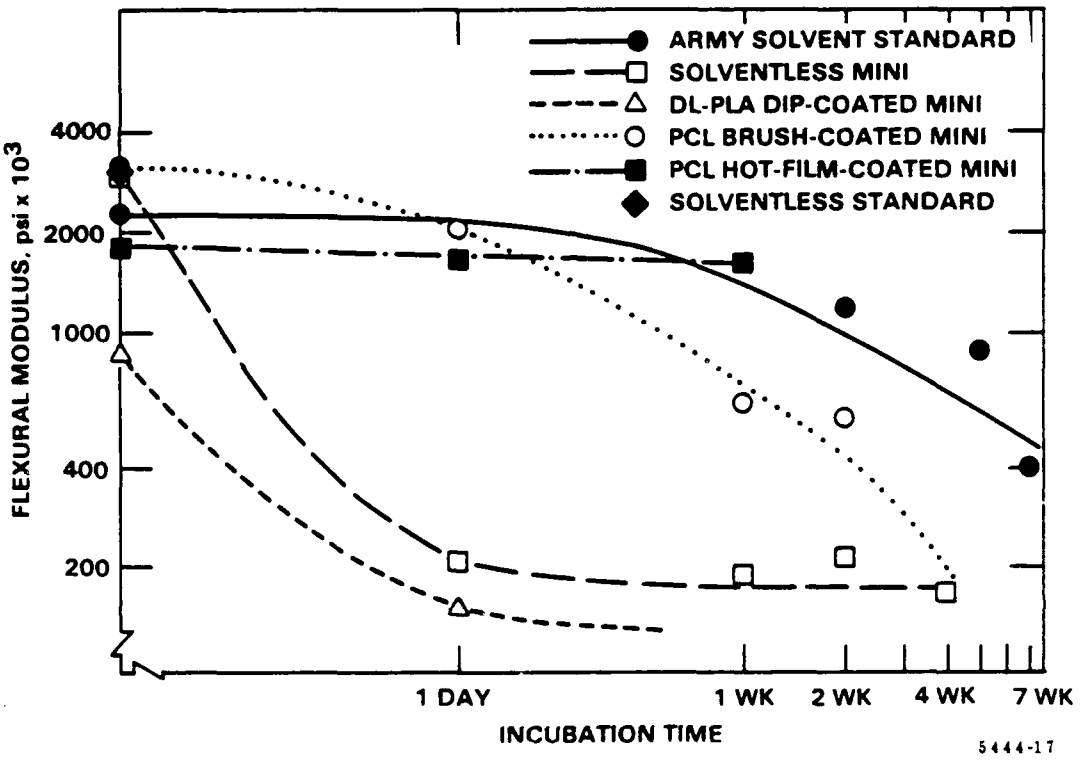


Figure 38. Logarithmic plot of flexural modulus loss of various formulations of DL-PLA/CMP composites after incubation in saline at 37 oC.

12. Evaluation of glass/polymer interface

Coating the composites did not completely protect them from environmental moisture, possibly a result of nicks, cuts, or imperfections in the coating, and additional measures were employed to maintain the integrity of the composite. We believed that a problem existed in the interface between the DL-PLA matrix and the CMP fiber. In order to achieve the benefits of both the polymer matrix and reinforcing fiber in a composite structure, the interface between these two phases must be intact and functional. In an effort to identify problems associated with DL-PLA as the polymer matrix, CMP as the reinforcing fiber, incompatibilities in our fabrication techniques, or other discrepancies in our regimen, we undertook an investigation in which both resorbable and nonresorbable materials were used in composite fabrication.

In this investigation, polypropylene and a cure-in-place thermoset epoxy were selected as nonbiodegradable matrix materials. DL-PLA and PCL were selected as the biodegradable matrix materials. PCL is more hydrophobic than DL-PLA in vivo, owing to its higher alkyl content and crystalline nature. Polypropylene and PCL were both thermoplastic and were processed similarly to DL-PLA. CMP was chosen as the bioresorbable reinforcing fiber for this study. Commercially available fiberglass (FG) was selected as the nonresorbable reinforcing material.

Using this test design, we were able to distinguish between the effects of reinforcing material, polymer-matrix selection, and fabrication techniques. Each composite was prepared using our standard techniques except when epoxy was used as the matrix. Thermoset epoxy composites were prepared by mixing the epoxy and hardener in the appropriate ratios and pouring the mixture over each layer of fiber. The mold was then gradually closed to remove excess epoxy.

After fabrication, each composite was cut into four mini plates of equal size and either tested as a control or incubated at 37 °C in PBS for either 1, 7, or 14 days. The mechanical properties of the composites were then evaluated in three-point bending. These results are recorded in Tables XXIV and XXV and illustrated in Figures 39 through 42. Table XXIV provides a record of the average values for both the changes in flexural modulus and strength. Table XXV provides these results as a percent of loss of flexural properties from the control values.

The data in Figure 39 show an interesting trend. All of the composites fabricated with CMP gave a dramatic decrease in flexural strength compared to those prepared with the FG. This was suspected to have been caused by the degradability of the CMP fibers, not due to differences in fiber diameter. It is also encouraging that the two most hydrophobic polymer matrices, polypropylene and PCl, gave better retention of flexural strengths than the more hydrophilic epoxy and DL-PLA resins even though their initial values were low. This indicated that the use of a more hydrophobic biodegradable polymer in conjunction with a more hydrophobic biodegradable glass would provide strength retention.

Figure 40 shows the same type of effect for the values of flexural modulus. All samples with the biodegradable CMP fibers gave sudden decreases

TABLE XXIV. LOSS OF FLEXURAL PROPERTIES OF GLASS-REINFORCED COMPOSITES AFTER INCUBATION IN PHOSPHATE-BUFFERED SALINE AT 37 °C AS A FUNCTION OF TIME

Sample Composition[a]	Flexural strength, 10^3 psi, during incubation period				Flexural modulus, 10^6 psi, during incubation period			
	Day 0	Day 1	Day 7	Day 14	Day 0	Day 1	Day 7	Day 14
E/FG	81	60	46	3	1.64	1.24	1.19	1.07
E/CMP	46	41	13	10	1.88	2.17	1.26	1.23
PP/FG	20	19	19	19	0.55	0.53	0.58	0.50
PP/CMP	16	9	9	9	1.07	0.62	0.41	0.26
PCL/FG	13	11	14	12	0.47	0.48	0.55	0.51
PCL/CMP	10	5	4	4	0.90	0.25	0.138	0.11
DL-PLA/FG	53	40	37	38	1.04	1.19	1.06	1.20
DL-PLA/CMP	41	8	6	5	2.90	0.20	0.22	0.25

[a] FG - fiberglass
CMP - calcium meraphosphate
E - epoxy
PP - polypropylene
PCL - polycaprolactone
DL-PLA - poly(DL-lactide)

TABLE XXV. PERCENT CHANGE OF FLEXURAL PROPERTIES OF GLASS-REINFORCED COMPOSITES AFTER INCUBATIONIN PHOSPHATE-BUFFERED SALINE AT 37 °C AS A FUNCTION OF TIME

Sample composition[a]	Flexural strength, % change from control, during incubation period			Flexural modulus, % change from control, during incubation period		
	Day 1	Day 7	Day 14	Day 1	Day 7	Day 14
E/FG	-25	-43	-59	-25	-27	-35
E/CMP	4	-67	-74	34	-18	-25
PP/FG	-6	-2	-2	-27	3	-8
PP/CMP	-46	-45	-47	-42	-62	-76
PCL/FG	-15	7	-3	0	15	8
PCL/CMP	-58	-59	-65	-72	-85	-88
DL-PLA/FG	-25	-30	-36	14	2	15
DL-PLA/CMP	-80	-85	-88	-93	-92	-91

[a] FG - fiberglass
CMP - calcium metaphosphate
E - epoxy
PP - polypropylene
PCL - polycaprolactone
DL-PLA - poly(DL-lactide)

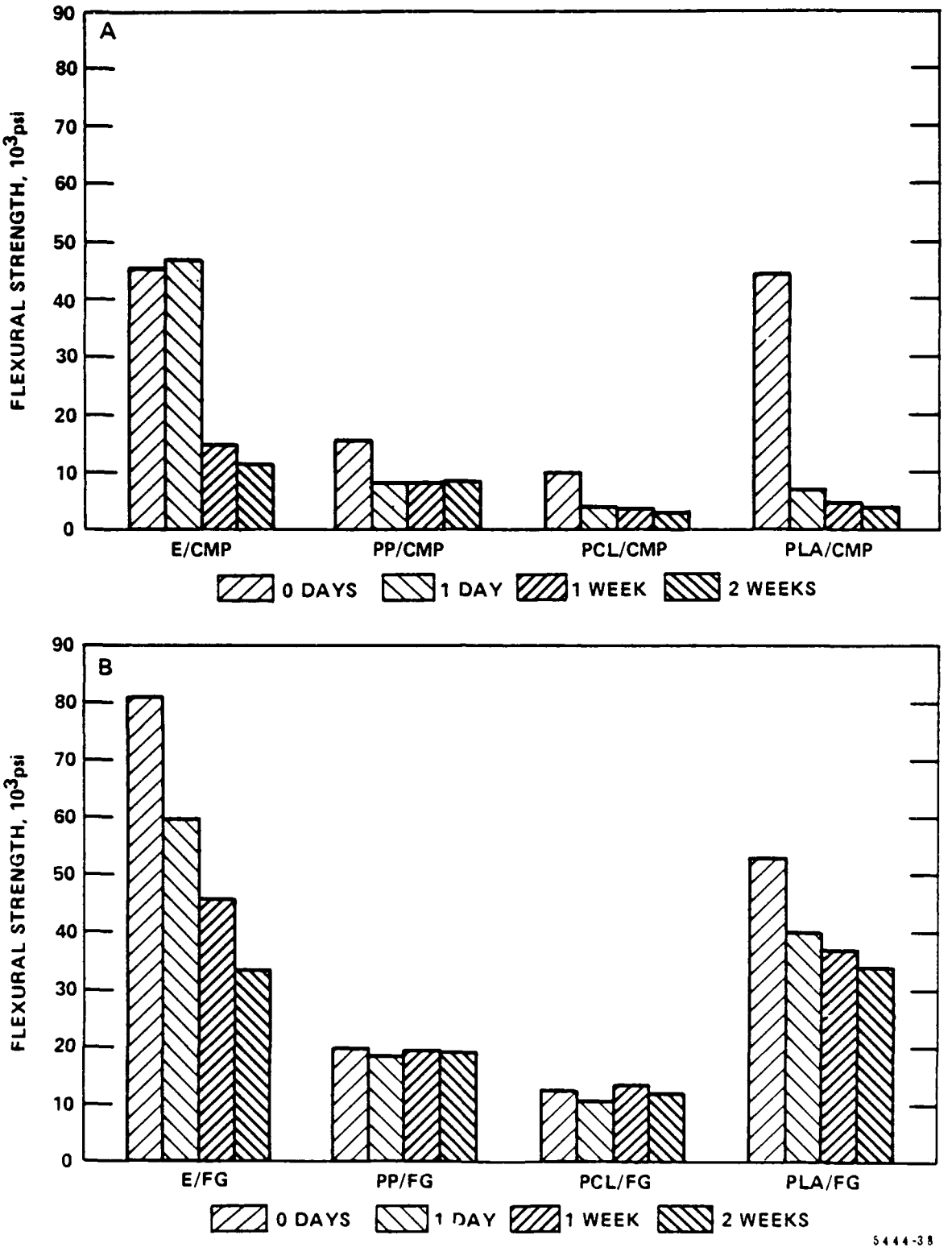


Figure 39. Flexural strength loss of epoxy (E), polypropylene (PP), polycaprolactone (PCL), and poly(DL-lactide) (PLA) matrix composites reinforced with calcium metaphosphate (CMP) or fiberglass (FG) fibers as a function of incubation time in phosphate-buffered saline at 37°C: A) resorbable reinforcement; B) non-resorbable reinforcement.

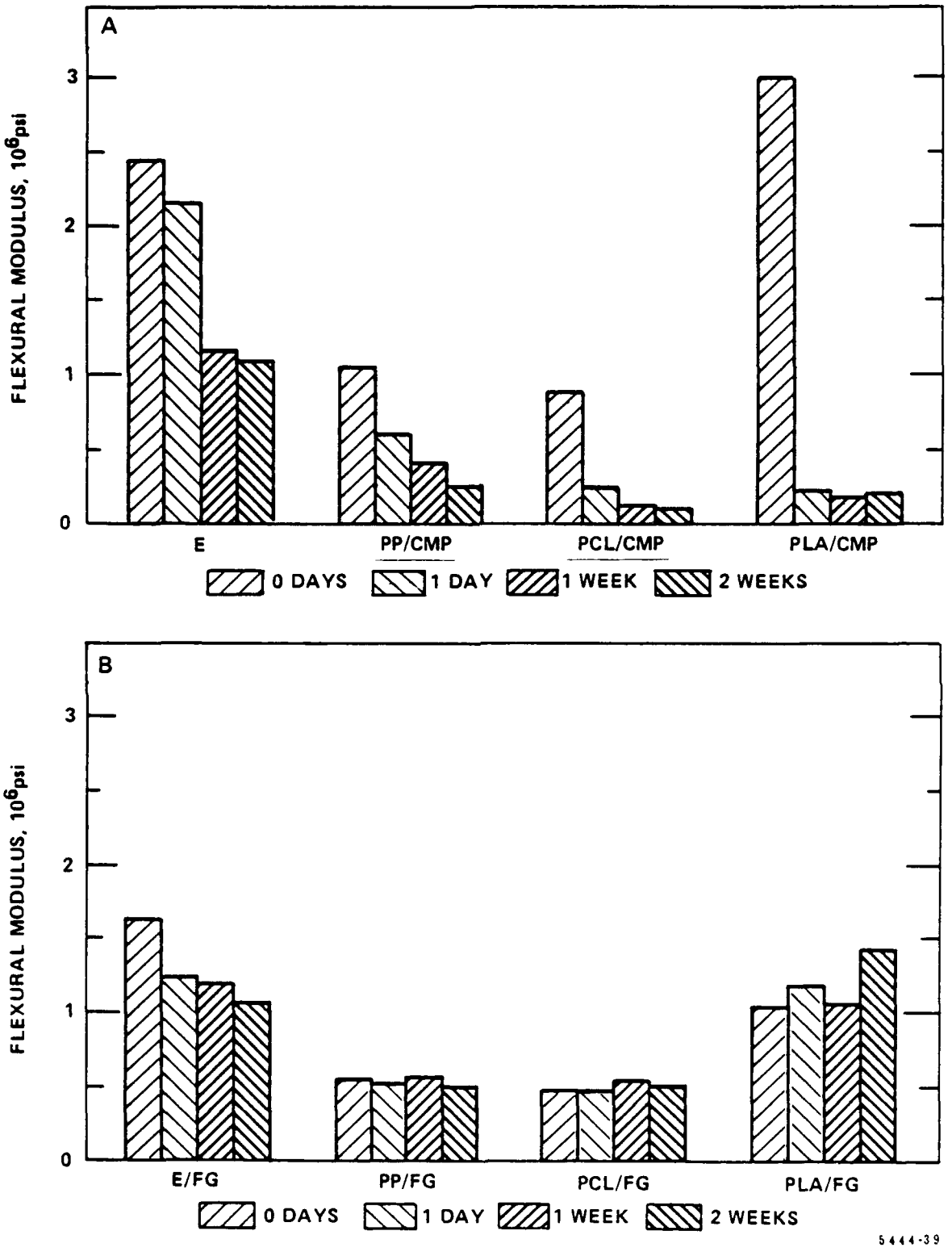


Figure 40. Flexural modulus loss of epoxy (E), polypropylene (PP), polycaprolactone (PCL), and poly(DL-lactide) (PLA) matrix composites reinforced with calcium metaphosphate (CMP) or fiberglass (FG) fibers as a function of incubation time in phosphate-buffered saline at 37°C: A) resorbable reinforcement, B) non-resorbable reinforcement.

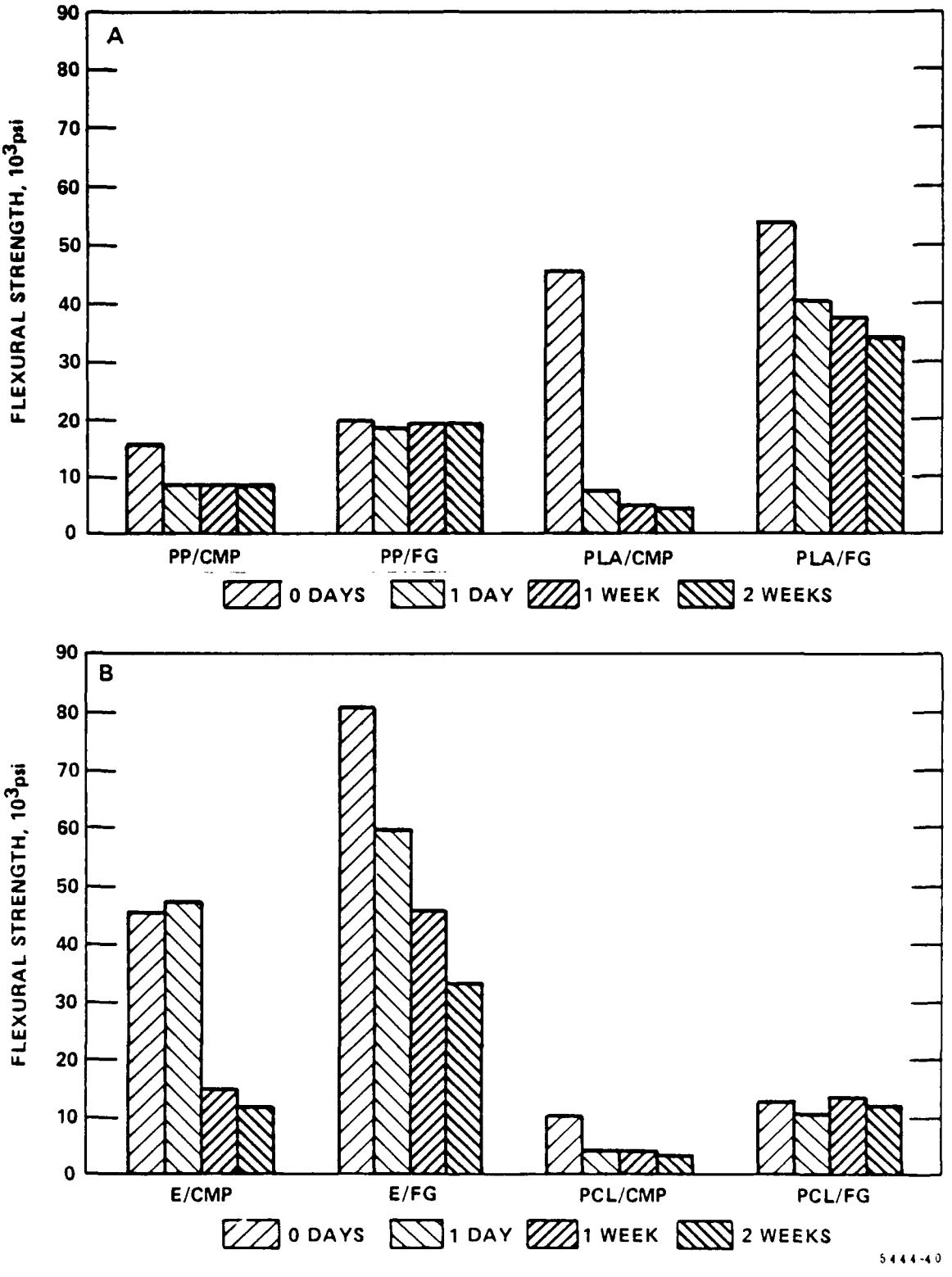


Figure 41. Decay of flexural strength of composites reinforced with calcium metaphospate (CMP) or fiberglass (FG) fibers as a function of incubation time in phosphate-buffered saline at 37°C: A) polypropylene (PP) and poly(DL-lactide) (PLA) matrices, B) epoxy (E) and polycaprolactone (PCL) matrices.

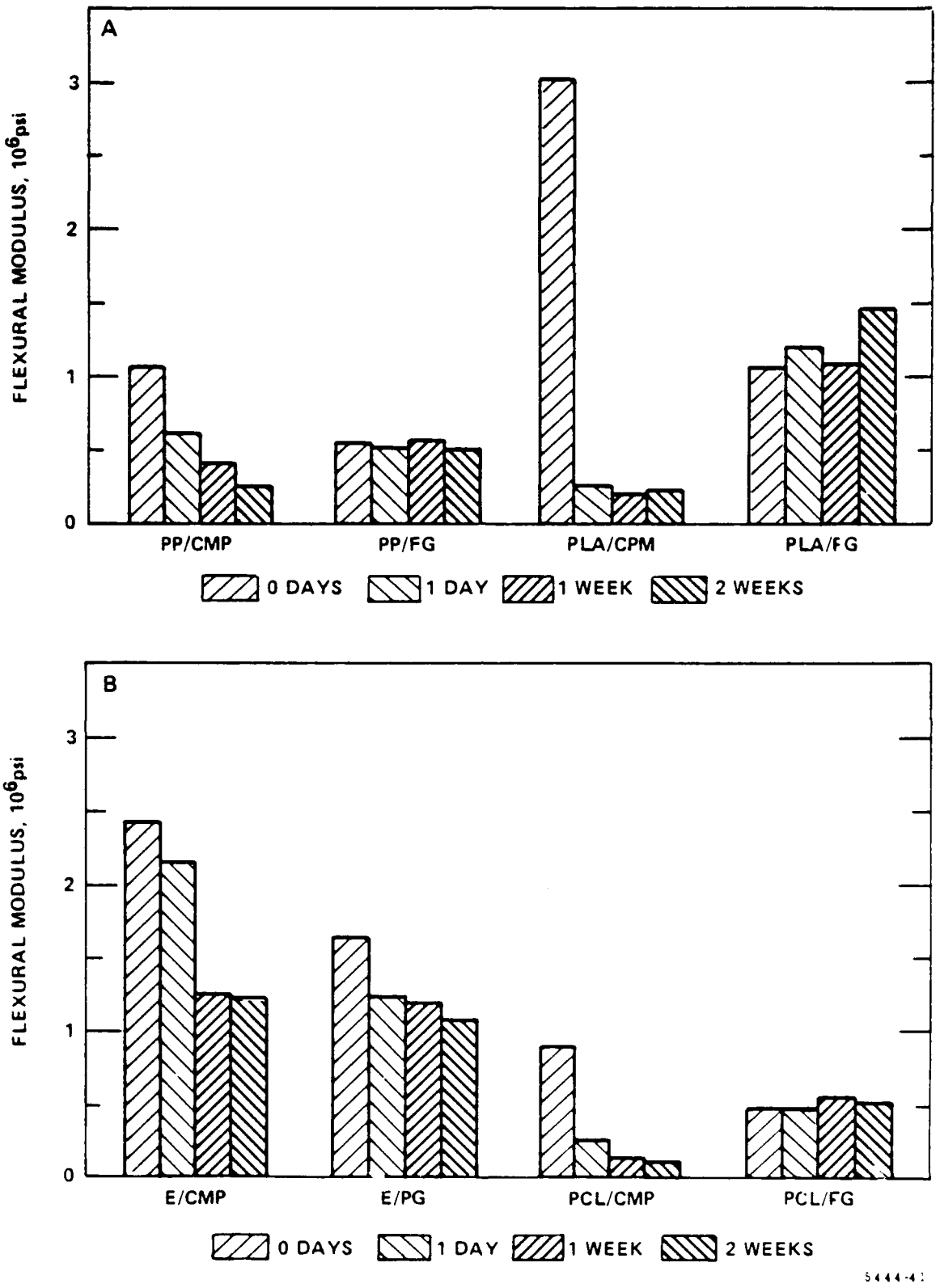


Figure 42. Decay of flexural modulus of composites reinforce with calcium metaphosphate (CMP) or fiberglass (FG) fibers as a function of incubation time in phosphate-buffered saline at 37°C: A) polypropylene (PP) and poly(DL-lactide) (PLA) matrices, (B) epoxy (E) and polycaprolactone (PCL) matrices.

in modulus values compared to the fiberglass samples, which showed almost no loss in modulus except for the epoxy resin.

These same results are shown in Figures 41 and 42 where the same resin with the two different fibers are plotted side by side. It is also evident that the smaller fiberglass fibers generally gave stronger composites than those prepared with CMP. The initial flexural modulus values shown in Figure 42 do not show the same relation as those for the flexural strengths; nevertheless, they still show the same decline with the biodegradable CMP fibers.

Our investigations to determine the effects of exposure of glass fiber ends on the degradation rate of the composite plates have been illustrated by comparing the differences in degradation rates of full-size plates (3 x 0.05 x 0.125 in.) as compared to the mini (or cut) plates (1.5 x 0.25 x 0.125 in.). DL-PLA composites reinforced with either fiberglass or CMP were used in this comparison (Figure 43). Initial values for both strength and modulus of full-size and mini plates are similar. Prolonged exposure of the fiberglass-reinforced plates to PBS does not catastrophically affect the strength of either the full-size or the mini plates, and in particular, the modulus of either of the plates. However, full-size and mini CMP-reinforced plates degraded appreciably with prolonged exposure to saline, with the mini plates degrading at a rate much faster than that of the full-size plates. The results of these studies confirmed our suspicions that exposed CMP fiber ends obtained with the cut mini plates or from other imperfections, such as drill holes, significantly affect the rate of fluids wicking into the composite, which adversely affects the mechanical properties of the composite.

13. Processes to create hydrophobic composites

In addition to those efforts described in the previous sections designed to retard fluids entering the composite, we also attempted to repel fluids by creating a hydrophobic environment within the composite structure. This was done by precoating the CMP reinforcing fibers with crystalline biodegradable polymers, investigating alternative biodegradable polymers, and using hydrophobic additives, such as surfactants and oils.

a. Development of a more hydrophobic matrix

Previous studies that the primary cause of the rapid loss of flexural properties seen in composites exposed to a moist environment was due to excess fluids wicking into the composites and ultimately destroying the polymer/glass interface. These studies indicated that the use of either a more hydrophobic polymer matrix may be required to eliminate or reduce fluid wicking into the composite. One method of increasing the hydrophobicity of the DL-PLA matrix was the use of a crosslinking agent. While crosslinking the DL-PLA to increase the hydrophobicity of the matrix was a feasible idea, it would also destroy the thermoplasticity of the polymer. This would require that the polymer be crosslinked during the final fabrication step. Because we could not accomplish this with our equipment, this technique could not be used with our composite process.

Another approach to provide a more hydrophobic matrix was to replace the hydrophilic DL-PLA matrix material with a more hydrophobic polymer. PCL and L-PLA are two biodegradable polymers that were known to be hydrophobic due to

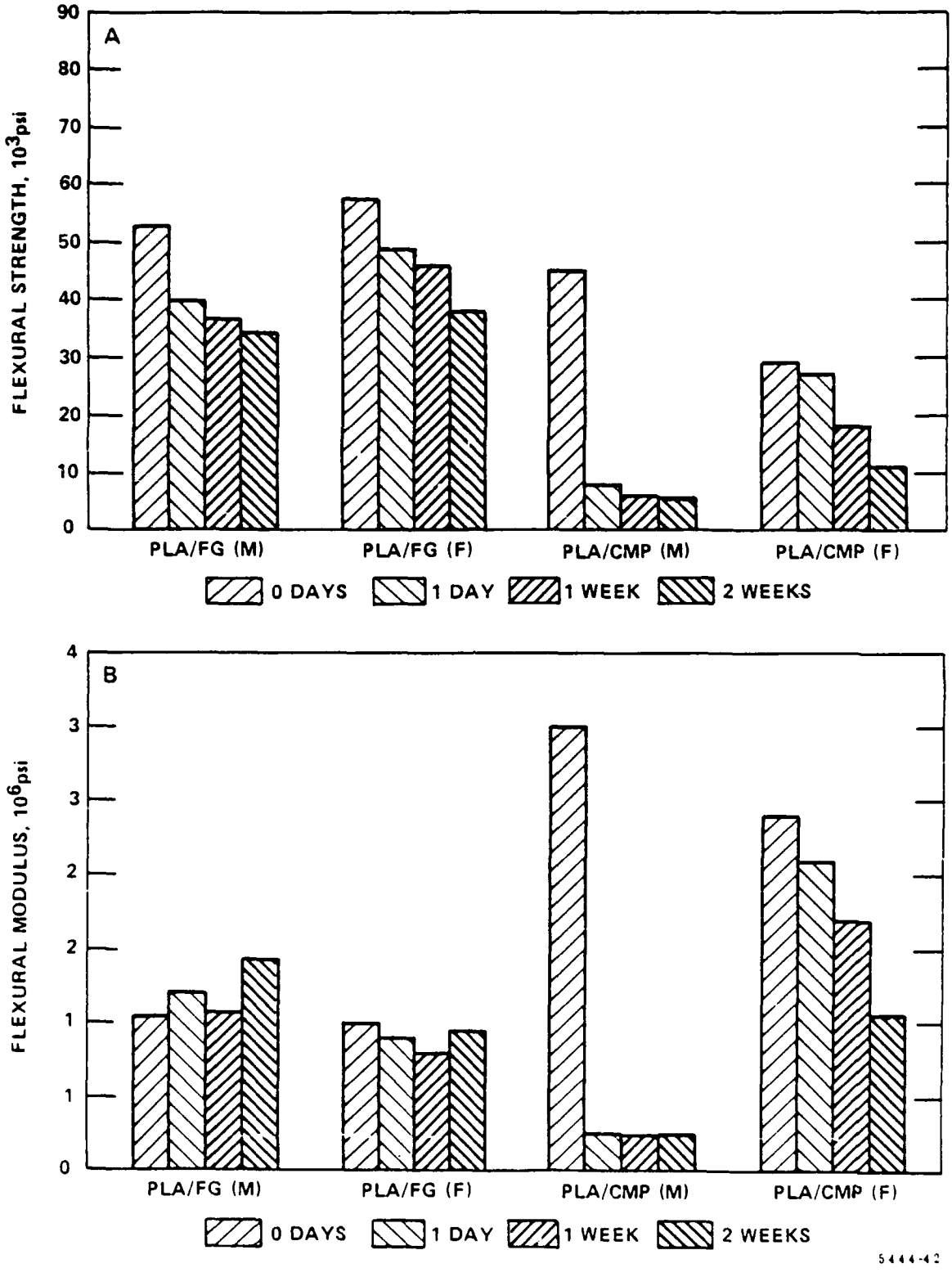


Figure 43. Comparison of flexural properties of full-size (F) and mi, (M) poly(DL-lactide) (PLA) composites reinforced with calcium metaphosphate (CMP) or fiberglass (FG) as a function of incubation time in phosphate-buffered saline at 37°C: A) flexural strength, B) flexural modulus.

their high degree of crystallinity. Because PCL processes quite easily, it was examined first. These plates, however, were excessively weak and easily deformed, and we then examined L-PLA. Because of its crystalline structure, L-PLA has poor thermal processing characteristics, and is more difficult to process than either PCL or DL-PLA. This made it difficult to prepare biodegradable composites with adequate polymer/fiber contact. Previously, we had shown that reducing the volume of CMP reinforcing fiber in DL-PLA composites from 65 to 35% provided better plate, and that this was probably a result of improved polymer/fiber contact, which reduced fluid wicking and better utilized the reinforcing fibers. We therefore decided to continue using 35% (by volume) CMP reinforcing fibers in our investigations of L-PLA composites.

Figures 44 and 45 show the flexural strength and flexural modulus of L-PLA composite plates fabricated using a variety of techniques. Our standard screening routine involved testing the composite plate in three-point bending to determine its initial flexural properties. The same plate or a similarly prepared plate were then used to prepare the mini plates. These plates were then tested in three-point bending, either before or after incubation in phosphate-buffered saline. It should be noted that this regime was used as a screening tool to determine which fabrication procedure resulted in the best strength/time profile under these conditions. Because the plates were cut and because some had been flexurally tested initially, this scenario represented a worst-case condition in that the mini plates contained exposed fibers, some of which had been prestressed. Earlier in the program, when we were dealing primarily with DL-PLA composites, we conducted some preliminary tests to determine the effects of testing mini plates as opposed to "standard" full-size plates (3 x 0.5 x 0.125 in.). We found then that the apparent flexural properties of mini plates were only slightly less than those of the standard plates. This was not the case for the plates reported in Figures 44 and 45, however, where an L-PLA matrix with an inherent viscosity of greater than 2.0 dL/g was used. Nonetheless, by using this type of screening tool, we were able to quickly determine the initial flexural properties as well as the relative decline of these properties under worst-case conditions.

The first set of data in Figures 44 and 45 shows the strength and modulus of L-PLA composite plates prepared using our solventless fabrication technique. The initial strength of these plates was only marginal and declined to nearly zero after only 10 days in saline. When the mini plates were cut, each of the 14 discreet CMP laminates could be distinguished, indicating that there was not good impregnation of the CMP reinforcing fibers by the L-PLA matrix. In an effort to obtain better polymer/fiber contact, we lightly sprayed each of the L-PLA/CMP laminates with a solvent before the composite was heat pressed. The result was a 140% increase in flexural strength (48×10^3 psi) and a 55% increase in modulus (3.9×10^6 psi) as shown in the second group of bars in Figures 44 and 45. These plates did much better in saline, maintaining about 50% of their strength after 10 days. We also prepared L-PLA/CMP composite plates where only a powder of the L-PLA was used as the matrix. These plates were prepared in a similar fashion to those described above, except that the L-PLA powder was distributed over each CMP laminate instead of a polymer film. The flexural strength and modulus of these plates was similar to those using the solvent bonding technique, both initially and after incubation in saline (third group of bars in Figures 44 and 45).

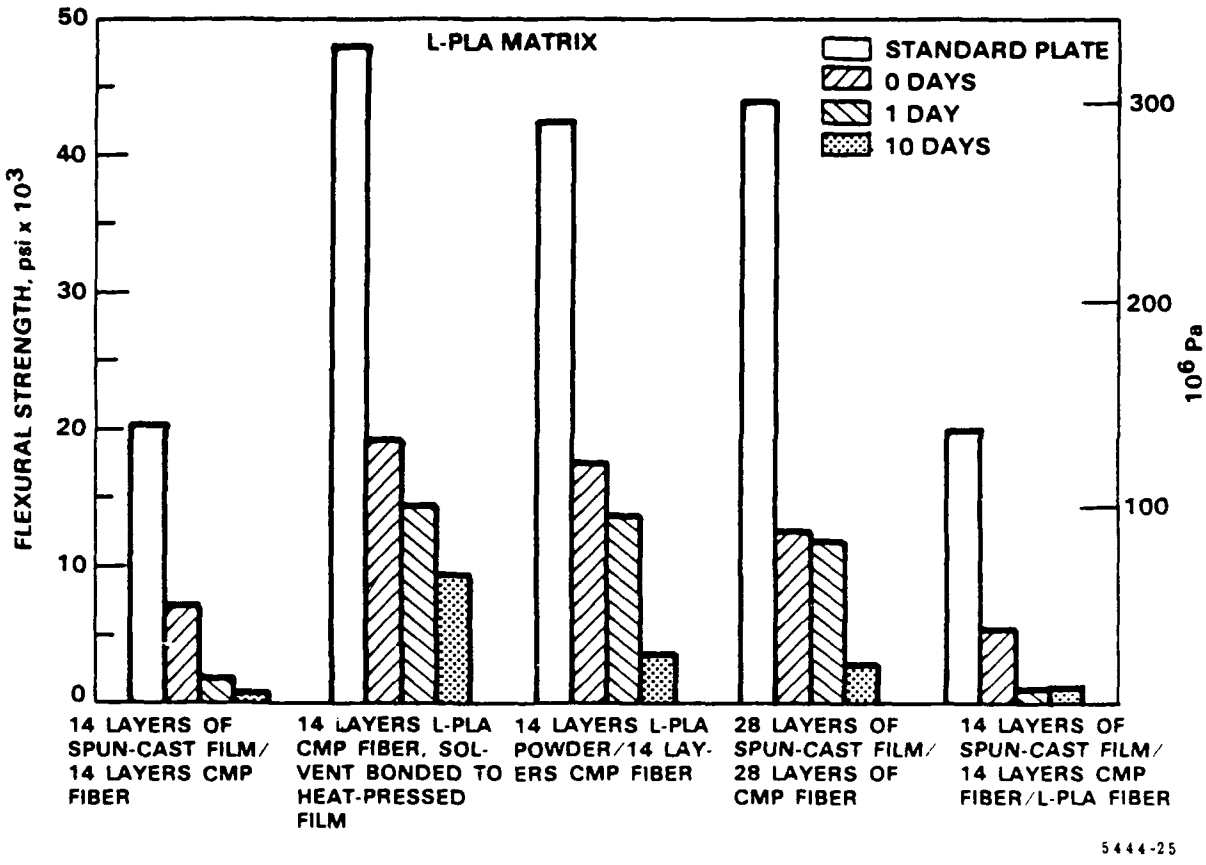


Figure 44. Comparison of the flexural strength of standard L-PLA/CMP (IV > 2.0) composite plates using different fabrication techniques and the rate of strength loss of mini plates after incubation at 37 °C in phosphate-buffered saline.

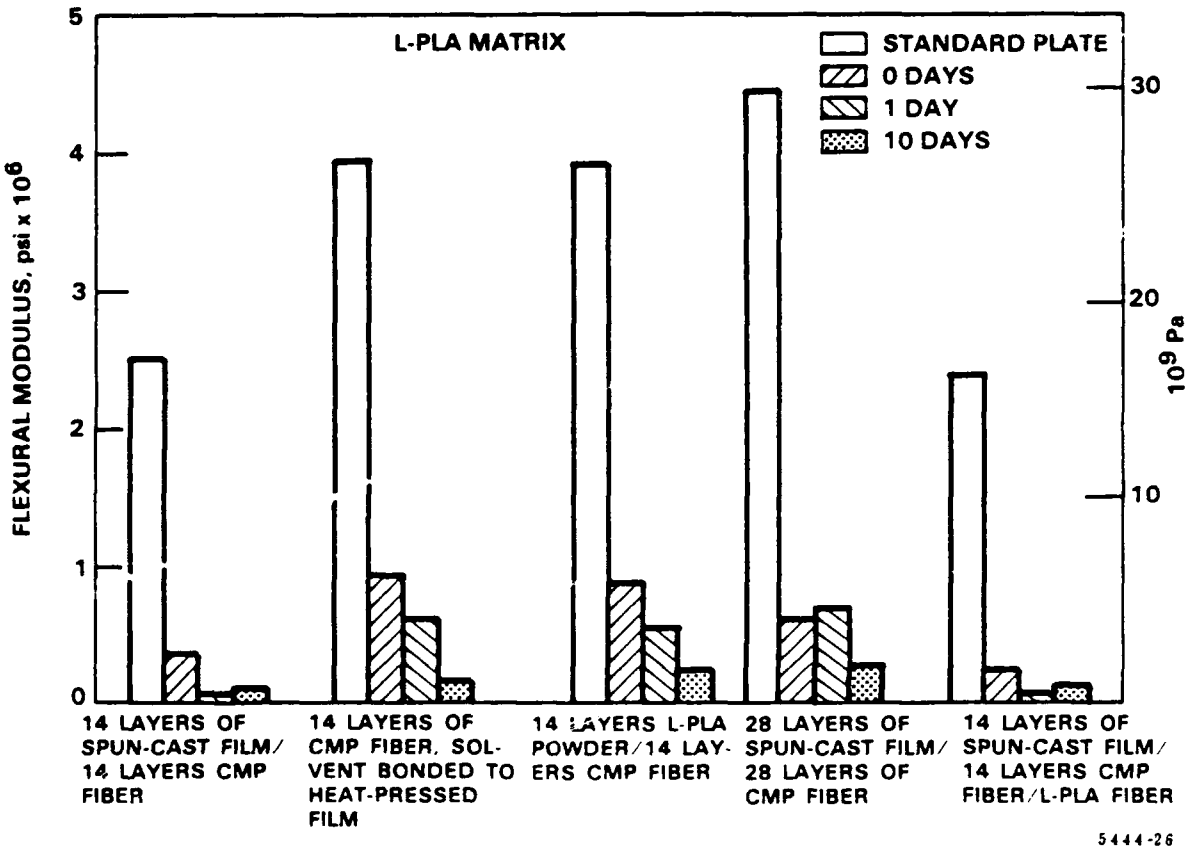


Figure 45. Comparison of the flexural modulus of standard L-PLA/CMP (IV > 2.0) composite plates using different fabrication techniques and the rate of strength loss of mini plates after incubation at 37 °C in phosphate-buffered saline.

Because of the problems we encountered in forcing the L-PLA matrix to impregnate and surround the CMP fibers, we prepared the next group of plates with thinner polymeric films, thereby allowing us to use twice as many laminates. These films were spun cast instead of heat pressed. Although twice as many laminates were used, the overall fiber loading of the composites remained at 35% (by volume). The results of three-point bending tests on these composites is shown in the fourth group of bars in Figures 44 and 45. These plates initially had very good flexural properties, and after incubation in saline, the strength and modulus declined at a rate similar to the solvent and powder composites described above.

The last group of composites prepared using this high-molecular-weight L-PLA involved using both L-PLA films and L-PLA fibers that were melt spun on our extrusion equipment for use in these plates. We had hoped that mixing the L-PLA fibers with the CMP fibers would result in better contact between polymer and CMP fiber. The matrix portion of the composites was divided equally between spun-cast L-PLA films and L-PLA fibers. The overall volume of CMP fiber remained at 35%. Again the strength and modulus of these composites were only marginal, being about half of that reported for the three previous groups of composites. The reasons for this poor performance are not clear but are probably related to the difficulty we had in manipulating the L-PLA fibers during composite fabrication.

b. The effects of sizing agent on the DL-PLA/CMP composites

In an effort to retard the influx of fluid into the composite plates and to consequently slow down the rapid loss of flexural properties of the composites, we attempted to coat a sizing agent onto the glass surface to enhance bonding between the polymer matrix and the glass reinforcing fibers. The sizing agent we used was Dow Corning's Z-6032 silane. Although this material is neither biodegradable nor biocompatible, we wanted to determine whether any sizing agent would bond the reinforcing fibers to the polymer matrix. If this task could be accomplished, reduced fluid wicking, better stress transfer, and greater fiber stability would probably result. Z-6032 possesses both organic and inorganic reactivity, which makes it an excellent coupling material because it can bond to both the organic matrix and the inorganic glass. It is supplied in methanol and can either be added to the matrix material or used as a typical coating on the glass surface. We chose to apply the silane to the surface of the glass to keep the concentration of the sizing agent in the composite plate to a minimum. Once the methanol was driven off, the fibers were laminated into both a DL-PLA composite and an L-PLA composite and the flexural properties of mini plates were examined as a function of incubation time in phosphate-buffered saline.

The results, presented in Figure 46, indicate that coating the reinforcing fibers with silane provides some improvement in the flexural strength and the modulus of DL-PLA composites after 1 week of incubation. The L-PLA plates were poorly laminated (when cut, discrete laminations could be seen) and conclusions based on the data may not represent actual enhancement. The flexural strength and modulus of the composites treated with silane show marked improvements for the 1 day values, but the 1 week values are not much different from the untreated controls. Because the initial strength and modulus of the composites does not increase substantially when the reinforcing fibers are treated with silane there is probably little or no chemical bonding

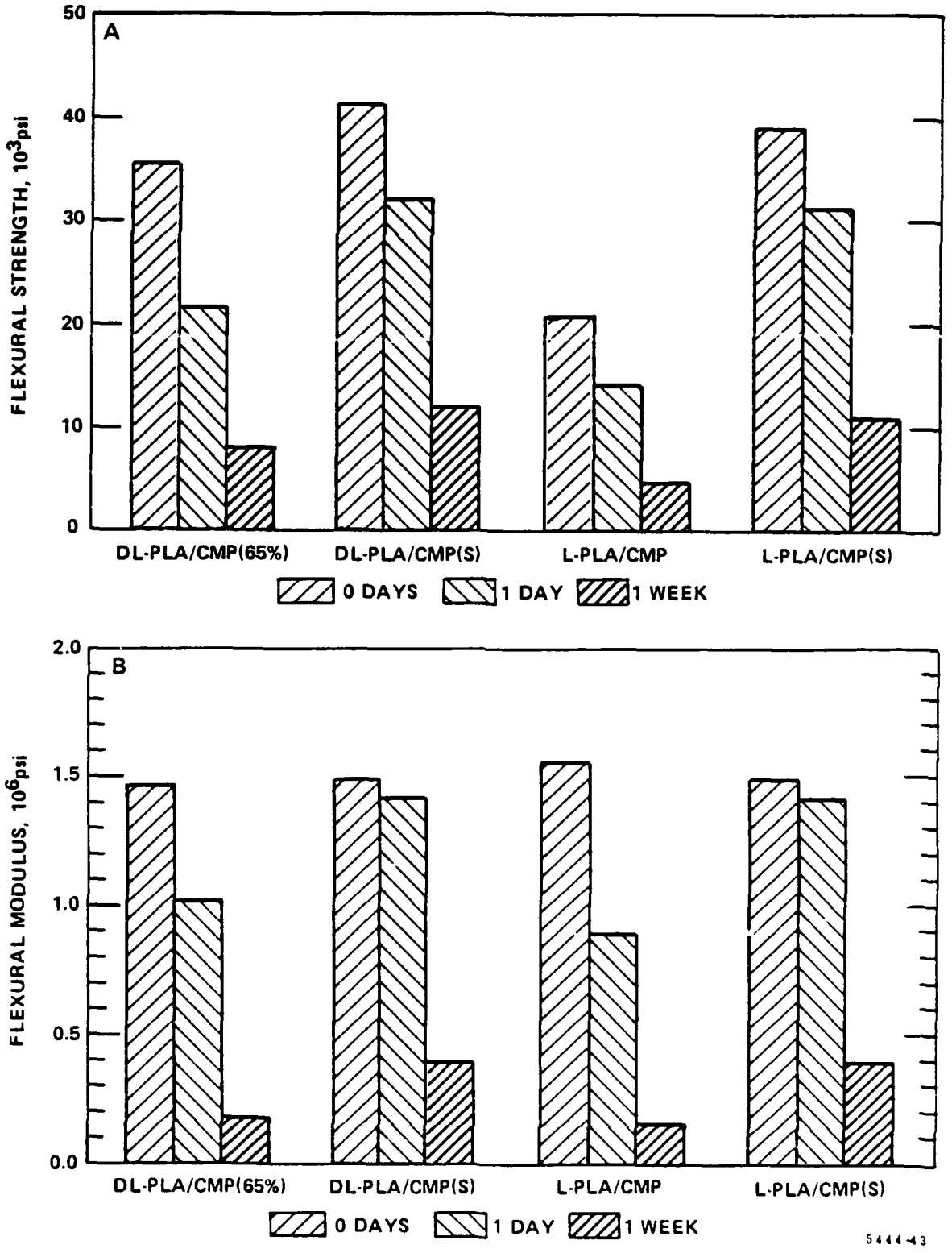


Figure 46. Change in flexural properties of Dow Corning Z-6032 coated [denoted by (S)] and noncoated 65% by volume CMP fiber-reinforced mini composites after incubation in phosphate-buffered saline as a function of time: A) flexural strength, and B) flexural modulus.

between the sizing agent and the polymer matrix. Evidence that the silane may bond with the CMP-reinforcing fibers comes from the slower decay of flexural properties (and thus protection of the surface of the reinforcing fibers) of the treated composites. Ultimately, however, the fluid wicks along the fibers and to destroy the weakly formed bonds of the silane glass interface, which resulted in composite weakening.

c. Coating of glass fiber with hydrophobic polymers

Because of the slight improvement in property retention using a sizing agent, our next attempt to prevent fluid from wicking along the glass/fiber interface of biogradable composites fiber was to precoat the CMP reinforcing fibers with a hydrophobic biodegradable polymer. We initially attempted to coat the fiber with a newly available hydrophobic copolymer of poly(hydroxybutyrate) (PHB) and poly(hydroxyvalverate) (PHV). We prepared a solution of the copolymer (PHBHV) in chloroform and coated the CMP reinforcing fibers by brushing each of the 14 layers and allowing the solvent to evaporate. These coated layers were then incorporated into an L-PLA matrix using our standard solventless technique. These plates did not form good laminates due to the poor processing properties of the L-PLA and the low melting point of the PHBHV copolymer. Similar processing problems were also encountered when PCL was used to coat CMP fibers because of the difference in melting points between the coating polymer and the matrix polymer. Although both PCL and PHBHV are hydrophobic, they melt at temperatures much lower than those for DL-PLA and L-PLA. Also because these polymers are hydrophobic, they do not readily wet the inorganic reinforcing fibers and thus yield weak composites.

We again prepared composites using PCL- or PHBHV-precoated CMP fibers, but this time the polymer used to coat the fibers was also used as the polymer matrix. The first two groups of data in Figures 47 and 48 illustrate the differences in the flexural strength and modulus of PHB/CMP or PHBHV/CMP composites before and after incubation in saline. The first group of bars represents the flexural properties of PHB/CMP composite plates; the second group of bars represents the PHBHV plates containing PHBHV-precoated fibers. The flexural properties of both the PHB and the PHBHV composites are far below those reported for the L-PLA plates shown in Figures 44 and 45. Similarly, composites using PCL as the matrix and fiber coating resulted in relatively weak plates. The results of three-point bending tests performed on these plates is shown in the third and fourth group of bars in Figures 47 and 48. The third group of bars represents the flexural properties of PCL plates that did not contain precoated fibers; the fourth group of bars represents PCL plates that contained precoated fibers.

The flexural properties of L-PLA composite plates containing CMP fibers coated with L-PLA is shown in the first set of bars in Figures 49 and 50. The L-PLA used to prepare these plates had an inherent viscosity less than 1.0 dL/g; therefore, these data are not directly comparable to that shown in Figures 47 and 48. However, because these plates were made in a similar manner to those whose flexural properties are shown as the second group of bars in Figures 47 and 48, the effects of this lower-molecular-weight polymer on flexural properties can be estimated. There was 50% reduction in flexural strength and modulus when going from higher-molecular-weight (IV > 1.0 dL/g) to a lower-molecular-weight (IV < 1.0 dL/g) L-PLA. Because this difference was not immediately apparent to us, this L-PLA was used in the evaluations

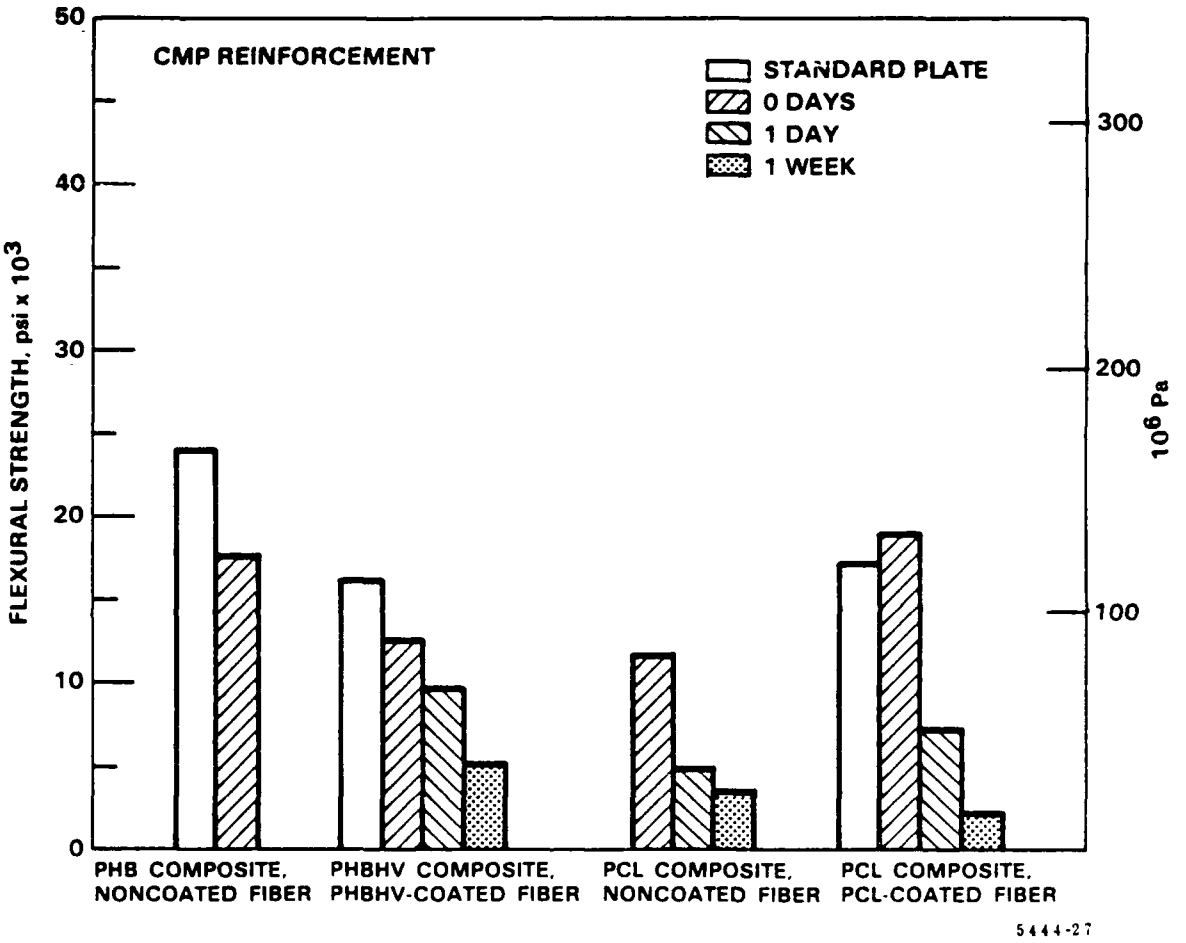


Figure 47. Comparison of the flexural strength of standard PHB, PHBHV, or PCL composite plates with noncoated or coated CMP fibers and the rate of strength loss of mini plates after incubation at 37 ^{0}C in phosphate-buffered saline.

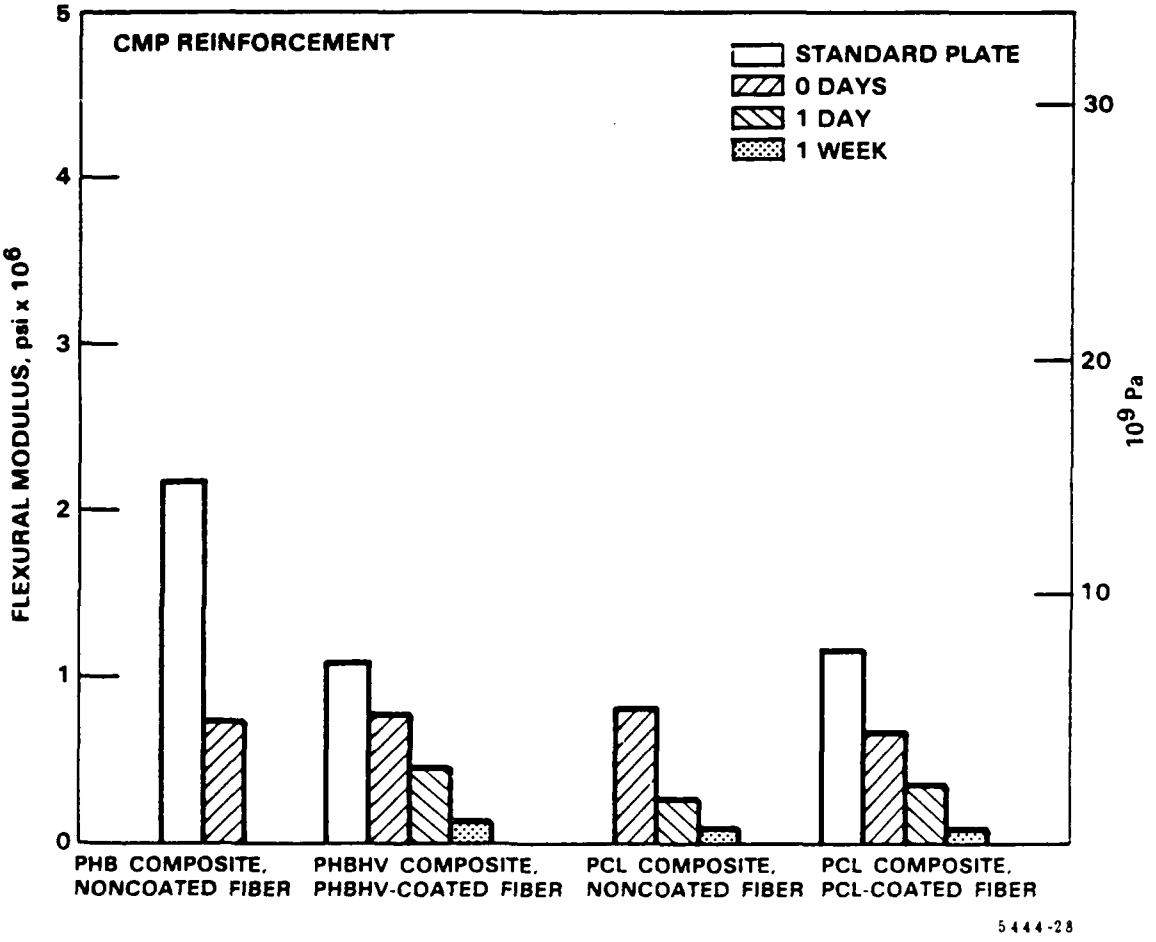


Figure 48. Comparison of the flexural modulus of standard PHB, PHBHV, or PCL composite plates with noncoated or coated CMP fibers and the rate of strength loss of mini plates after incubation at 37 °C in phosphate-buffered saline.

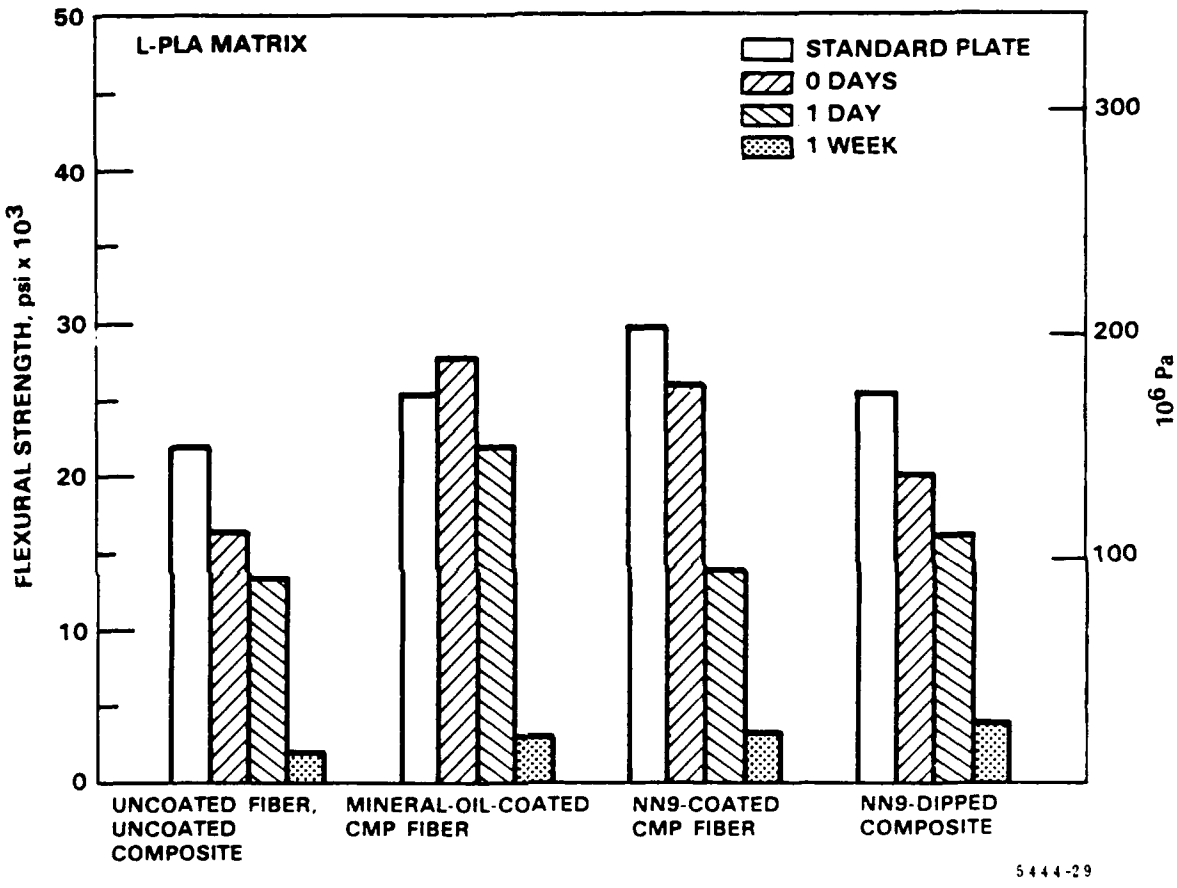


Figure 49. Comparison of the flexural strength of standard L-PLA/CMP (IV < 1.0) composite plates fabricated with or without mineral oil or nonoxynol-9 and the rate of strength loss of mini plates after incubation at 37 °C in phosphate-buffered saline.

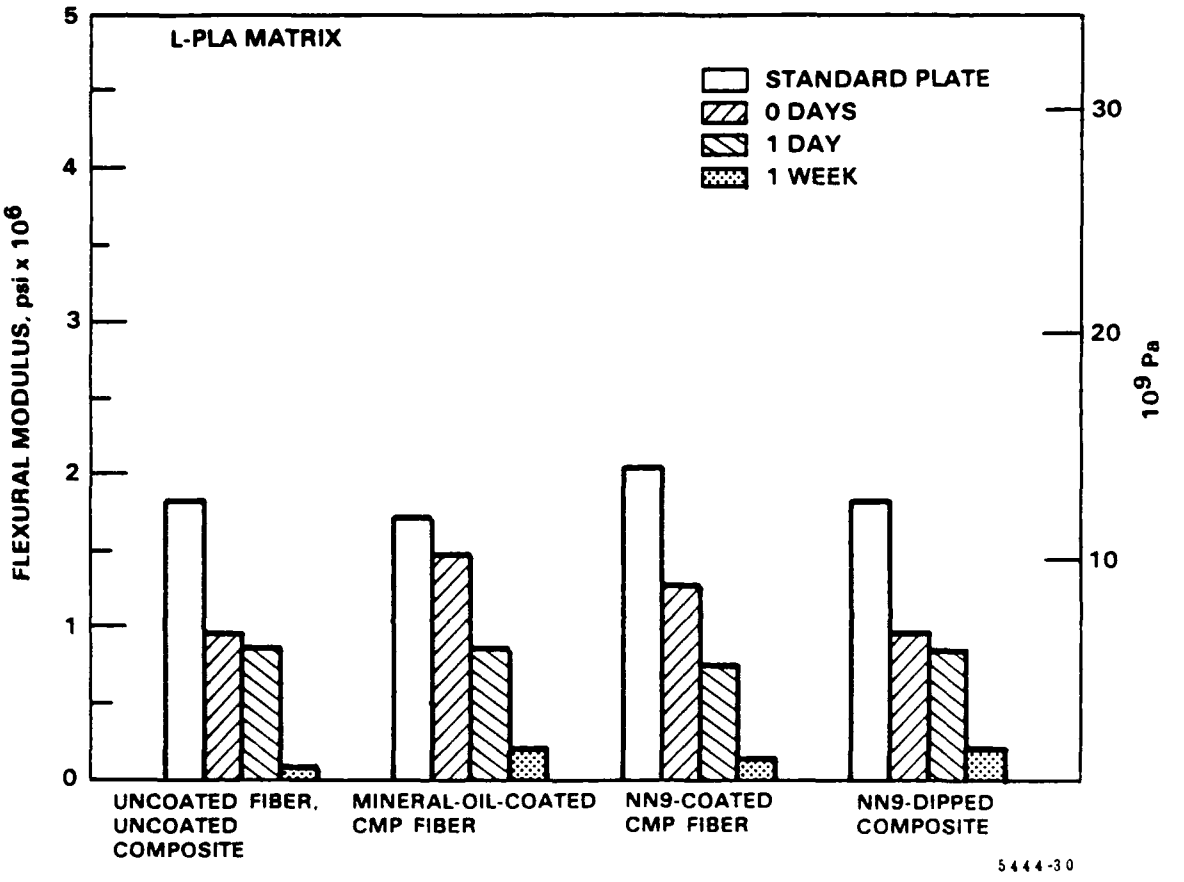


Figure 50. Comparison of the flexural modulus of standard L-PLA/CMP (IV < 1.0) composite plates fabricated with or without mineral oil or nonoxynol-9 and the rate of strength loss of mini plates after incubation at 37 °C in phosphate-buffered saline.

described in the following paragraphs and can only be gauged with respect to the data shown in Figures 49 and 50 and not those shown in Figures 47 and 48. We expected that the effects of hydrophobic additives on the flexural properties of biodegradable polymers, as described below, would hold true for the higher-molecular-weight L-PLA as well. Because we had reported better mechanical properties using lower-molecular-weight DL-PLA previously (using nonresorbable reinforcing fibers) and because the lower-molecular-weight L-PLA was more easily processed than the higher-molecular-weight L-PLA, we did not anticipate such a reduction in mechanical properties (4). We also noticed that mini plates cut from composite plates using the low-molecular-weight L-PLA did not show the same drastic reduction in strength as do those cut from the higher-molecular-weight plates.

Our final efforts to create a hydrophobic environment within and around the composite structure, were to use mineral oil or the surfactant nonoxynol-9 (NN9) to precoat the CMP reinforcing fibers. Both of these additives resulted in an increase of flexural properties for L-PLA plates, although the increase was not drastic. The results of three-point bending tests on composite plates fabricated with mineral oil or NN9 are shown in the second and third groups of bars in Figures 49 and 50. In addition to the slight increase in initial flexural properties when these hydrophobic coatings were used, the rate of strength decline after incubation in saline was somewhat slowed.

Another set of L-PLA plates (IV < 1.0) was prepared and dipped in NN9 before being tested. It was hoped that the NN9 would wick or diffuse into the composite and thus prevent rapid permeation by saline. The last group of bars in Figures 49 and 50 shows that coating the entire composite with NN9 did not greatly affect the initial flexural properties of the composites, nor did it alter the rate of strength decline.

Although biodegradable composite plates consisting of L-PLA as the matrix and CMP as the reinforcing fibers described here continued to lose their strength at a fairly rapid rate after incubation in saline, we believed that properly constructed full-size plates with an exterior coating of PCL would provide the strength/time profile necessary for effective fracture fixation in dogs. We had demonstrated that very strong biodegradable plates could be made with the proper selection of polymer molecular weight and fabrication process. We had also shown that DL-PLA plates coated with an exterior layer of PCL helped retard the influx of fluids and thus provide higher strengths for longer periods. Therefore, this combination of high-molecular-weight L-PLA and construction techniques led to the improved polymer/fiber contact, obtained with the plates used in the final in vivo evaluation.

14. Crystallization of CMP Fibers

In general, glasses that are crystallized are less soluble than their noncrystalline counterparts. We therefore tried to crystallize CMP already in fiber form, so that the reinforcing phase of the biodegradable composites would be less susceptible to fluids. Although most glasses crystallize only at temperatures above their glass-transition temperature (T_g), CMP has been reported to rapidly crystallize at temperatures below its T_g (4-6).

Unfortunately, this rapid crystallization was only seen in bulk samples. However, if crystallized under stress or under a temperature gradient, the

rate of crystal formation was accelerated. We tried to crystallize CMP fibers by stressing them at 8 kg/cm^2 while holding them under a temperature gradient of 20 °C/cm. Although these were the reported optimum conditions for crystalline growth in CMP, we were not able to detect crystal formation, and many of the fibers broke under these conditions. There is an abrupt change in crystal growth rate that occurs for specimens with thicknesses above 1 mm. The CMP fibers we were trying to crystallize had diameters of about 50 μm. The crystal growth rate of thicknesses can be $10\mu^7$ to $10\mu^8$ times slower than that of block specimens, even under optimal conditions. Although we were able to crystallize bulk samples of CMP in the past, it was not possible to form small-diameter fibers from bulk crystalline CMP. Therefore, we discontinued this phase of research.

15. Investigation of alternative bioresorbable glasses

To further improve the strength and degradation rate of the composite by improving the fiber/matrix interface, we examined the use of two glasses with previous histories as reinforcers for polymeric medical devices. The first of these was a glass prepared from sodium phosphate monobasic monohydrate (U.S. patent 4,612,934). The second was a glass prepared from a mixture of calcium oxide, calcium fluoride, and phosphorous pentoxide (U.S. patent 4,604,097). We prepared fibers of both of these glasses using our old drawing procedure and evaluated their tensile strength and dissolution rate in saline.

We have also experimented briefly with calcium sodium metaphosphate fibrils (U.S. patent 4,346,028). Because it was grown as small crystals, it was not available in continuous lengths and was more suited for use in injection-molding applications. It was reported to be water insoluble, yet it was broken down in the body through enzymatic attack.

We obtained a small sample of this material and tried to injection mold it with PCL. Parts formed using these materials had good surface quality upon visual inspection but were very brittle. Therefore, we abandoned the use of this glass as a reinforcing material.

16. Evaluation of screw holes on composite strength

Resorbable fixation plates are generally attached with bone screws, which required that transverse holes be drilled in the plates to accommodate these screws. To determine the effect of these holes on composite strength, we conducted a series of tests where holes were drilled through DL-PLA/CMP composites. Holes were drilled in our composite plate to accommodate a 6-32 machine screw. All holes were along the longitudinal axis of the plates, and either two or four holes were tested. In addition to accessing the effects of holes on the flexural properties of composite plates, we also investigated the differences between simple straight-through holes and counter-sunk holes. Half of the plates were securely attached to wooden splints to simulate attachment to bone. The other plates were tested without the use of the wooden splints. The splints were two discrete pieces of wood, therefore, the strength of the wood was not a major factor in stress and modulus calculations. The flexural properties of the plates and the plate/splint constructs were determined in 3-point-bending.

Figure 51 shows the effects of using two or four holes, attachment of the plate to the wooden splints, and counter-sinking the screw holes on the flexural strength and modulus of composite plates and plate/splint constructs. For all of the data presented in Figure 51, the standard equations for computing flexural strength and modulus were used. These equations are not completely valid because the screw holes alter the cross-sectional shape of the plates and the wooden splints change the force distribution on the plates and complicate the geometry of the applied load. Nonetheless, we used these equations because they allow us to compare the overall strength of the different systems under test.

There were several definite trends which can be seen in both the strength and modulus data shown in Figure 51. First, the values for composites attached to the wooden splints were always higher than those for the plates tested alone. This was due to the altered stress state created by the 6-32 screws and the presence of the wooden splints. Second, the plates which contained only two holes (either straight through or counter sunk) and not attached to the wooden splints were always stiffer and stronger than the corresponding plates containing four holes. This was expected because of the four-hole plates had more of the load-carrying material drilled out. Third, the plates and constructs which had counter-sunk holes were always less rigid and weaker than the same systems with straight-through holes. Again, this was due to the fact that the plates without counter sinks were more intact than the plates with counter-sunk holes. All of these trends are consistent for both strength and modulus calculations. However, when comparing differences between the strength and modulus of four-hole versus two-hole plates attached to the wooden splints, the trends are different. For these cases, the modulus of the plate/splint constructs with four holes was always higher than those with two holes. Conversely, the strength of plate/splint constructs with four holes was always lower than those with two holes. Because this trend was only seen when the plates were not tested with the wooden splints, the increased modulus for the four-hole constructs must be caused by the added effective rigidity of the wooden splints due to attachment of the additional screws. Similarly, this added rigidity concentrated the bending stresses near the center of the plates and resulted in an apparent lower strength.

Because the use of four hole instead of two resulted in constructs with higher rigidity and because counter sinking the screw holes detrimentally affects the strength and stiffness of the plate/splint construct, we recommended that a 4-hole attachment technique using straight-through holes be used in subsequent animal studies.

17. Torsional strength of composite plates

When the drilled composites were implanted in the animal studies, they tended to fracture along the longitudinal axis (through the screw holes) due to lack of reinforcing fibers in the orthogonal directions. Because the torsional loads in fixation plates can be greater than those in bending, laminates containing 45° cross-plies were evaluated. Based on an analysis of the stresses in a plate under complex loading, the normal bending stresses are predominately acting near the outer surfaces and dissipate near the interior. The maximum shear stresses caused by torsion are also at a maximum near the outer surface but do not diminish or change signs within the interior of the plate. For these reasons, we decided to concentrate the 45° cross-plies

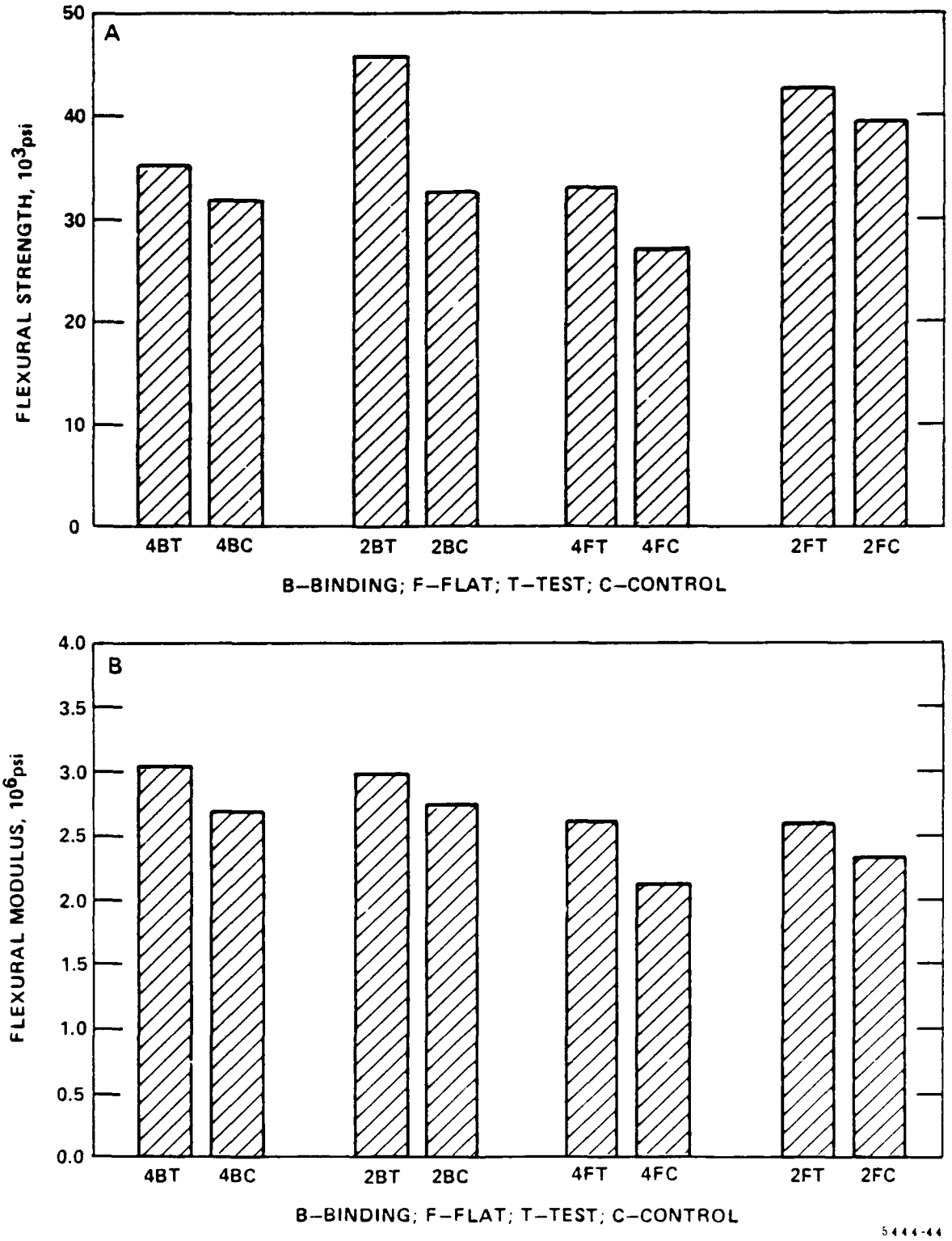


Figure 51. Effects of screw holes on the flexural properties of DL-PLA/CMP fiber-reinforced composites: A) flexural strength, and B) flexural modulus.

closer to the plate's neutral axis (with respect to bending). Because our standard laminating technique involved the lay-up of 14 layers of fibers, we chose the following configuration for torsionally resistant plates.

Layer:	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Laminate orientation:	0°	0°	0°	45°	0°	-45°	0°	0°	-45°	0°	45°	0°	0°	0°

So that two consecutive laminates do not have fibers with perpendicular orientations, at least one layer of longitudinal fibers was included between cross-ply laminates. The initial composite samples were prepared by coating fiber layers positioned at either 45° or 90° angles with a solution of PCL to maintain their orientation and protective CMP fibers. The solvent was removed from the fiber layer and composites were prepared by our standard stet techniques using 14 layers of fiber reinforcement.

In addition to the 45° and 90° oriented samples, 2 sets of controls plates were also prepared. The first control was a standard DL-PLA/CMP composite plate. The second set of controls had four 0° layers (layers 4, 6, 9, and 11) of PCL-coated fiber.

The apparent shear was calculated by the following equation:

$$G = 917\ TL/ab^3\mu\Phi$$

where:

G = apparent shear modulus of rigidity
T = applied torque,
L = specimen span length,
a = specimen width,
b = specimen depth,
Φ = angle of deflection, °
$\mu = 5.33-[3.36b/a(1-b^4/12a^4)] = 4.49$

The maximum shear stress was calculated using the equation

$$\tau = 2\ G\ \theta\ a$$

where:

τ = maximum shear stress, psi
θ = angle of deflection per unit length, radians/in.

Both controls and cross-ply composites were then evaluated in pure torsion using an in-house constructed torsion tester. This apparatus was mounted in our Instron Universal Testing Machine where the torque was applied and measured. The angle of twist was also recorded using a strip chart recorder. The results of these evaluations are presented in Table XXVI and illustrated in Figure 52.

These data show that the composite plates containing the cross-ply laminates exhibited lower torsional strength and modulus than the control plates containing unidirectionally oriented fibers only. This was believed to have resulted from shifting of the cross-ply layers during plate fabrication and

TABLE XXVI. DETERMINATION OF TORSIONAL STRENGTH OF COMPOSITES

Composite[a]	Shear modulus, psi	shear stress μ, psi
PLA/CMP	68,588	56,139
±45° PLA/CL	40,796	47,086
±45° PCL	26,904	45,287
PLA/CL	75,572	55,807
90° PLA/CL	30,420	31,171

[a] PLA/CMP - CMP-fiber-reinforced poly(DL-lactide) matrix.
±45° PLA/CL - ±45° polycaprolactone-precoated, CMP-fiber-reinforced, poly(DL-lactide) matrix.

±45° PCL - ±45° polycaprolactone-precoated, CMP-fiber-reinforced, polycaprolactone matrix.

PLA/CL - polycaprolactone-precoated, CMP-fiber-reinforced,poly(DL-lactide) matrix.

90° PLA/CL - 90° polycaprolactone-precoated, CMP-fiber-reinforced, poly(DL-lactide) matrix.

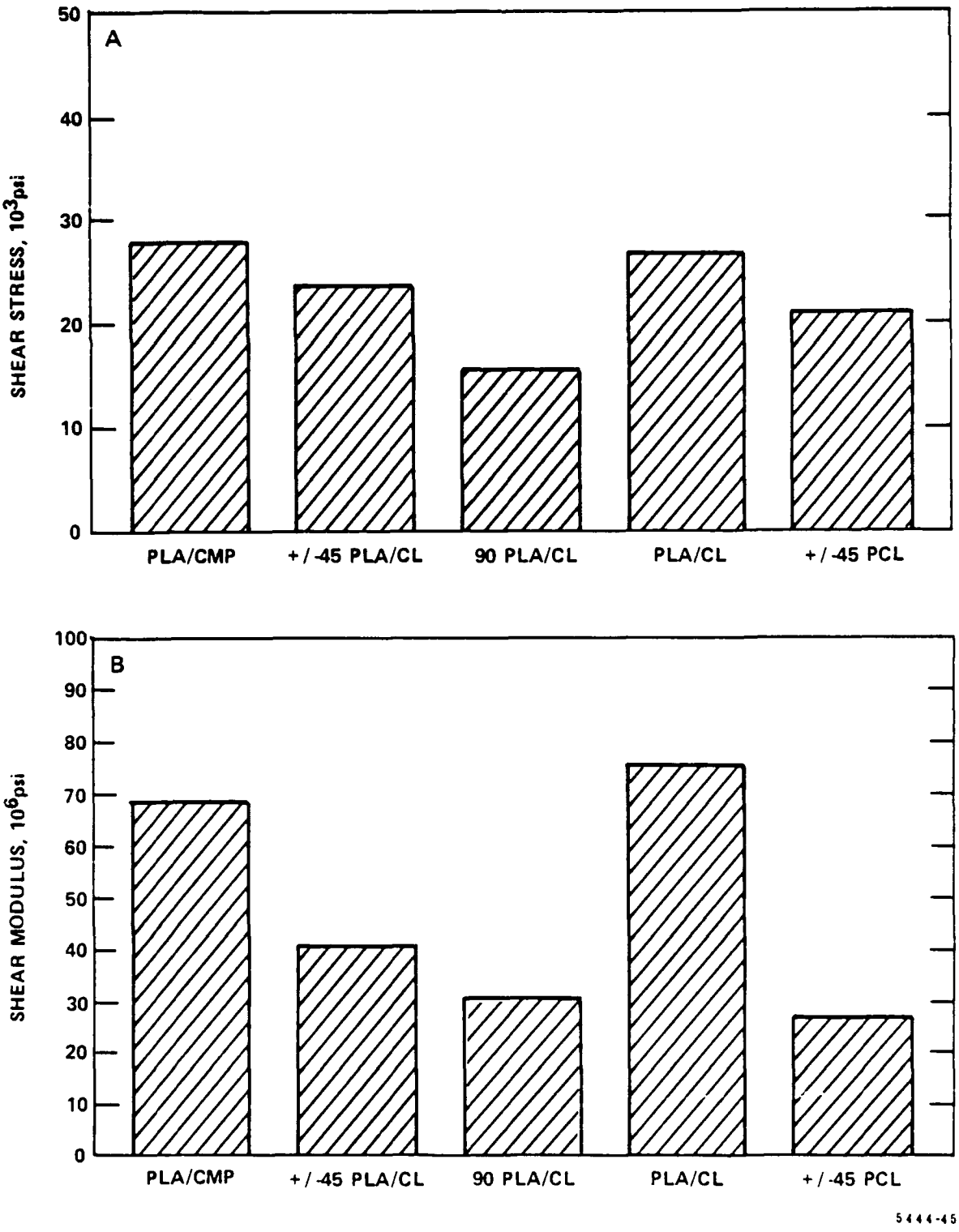


Figure 52. Torsional properties of cross-ply and control composites: A) sheer stress, and B) shear modulus.

concentrated them near the ends of the plates. This primarily resulted from differences between the melting and softening temperatures of DL-PLA matrix and the PCL used as the fiber coating. While fabricating the composite, the DL-PLA had to be heated to approximately 175 °C to obtain an adequate DL-PLA melt-viscosity. At this temperature, which was well above the melting point of PCL, the PCL became fluid and was easily displaced during the pressing of the composite plate. Because the venting ports for the removal of excess polymer were located at the ends of the composite mold, and because the cross-ply reinforcement was contained within the PCL layers, many of the cross-ply fibers may have migrated toward the ends of the plate when it was pressed or may have become jumbled or broken in their orientation. Moreover, we have previously reported that composites prepared using PCL as the matrix polymer did not have good rigidity or stiffness. Because of its inherent hydrophobicity, PCL does not readily wet the CMP reinforcing fibers and may not be suitable for use as either the matrix polymer or as a coating on the reinforcing fibers. Further evidence substantiating these conclusions comes from examining the torsional performance of cross-ply composites when PCL was used as the matrix polymer. When compared to identically prepared DL-PLA/CMP composites, these PCL-matrix composites were weaker and more compliant in torsion.

We were surprised to find that the composite plates containing only unidirectional and longitudinal CMP fibers were stronger in torsion than plates containing 45° cross-plies. These results cannot be reasoned from a mechanical-stress analysis using composite theory. Therefore, we concluded that the reason for the poorer performance of the cross-ply composites were probably related to an incompatibility between the reinforcing and matrix phases of the composite, the use of relatively large reinforcing fibers or discrepancies in our fabrication techniques. Material incompatibility may stem from the simultaneous use of hydrophobic and hydrophilic polymers, and difficulties we encountered in fabricating these composites were described earlier. These composite plates were prepared before we were able to make small-diameter CMP fibers on a consistent basis. The use of small-diameter CMP fibers and only one hydrophobic matrix material we believed would produce plates with equal or greater torsion strength than unidirectional plates. For this reason, and because longitudinal fracture of composite plates used in vivo is likely to remain a problem when only unidirectionally oriented fibers are used, we incorporated cross-ply layers into composite plates used in subsequent animal investigations.

18. Fabrication of composite plates for use in animal studies

Having developed several techniques which, when used independently, slightly improved property retention of our composite plates in vitro, we then established a fabrication process for the lamination of bone plates to be used by the Army for repairing mandibular fractures in dogs. The fabrication technique using 28 laminates (as opposed to the 14 used initially) was probably successful at improving composite properties because of the shorter distance the polymer had to flow to reach all of the CMP fibers during heat processing. Although the number of laminates was doubled, the total volume of material remained constant because each laminate contained only half of the mass contained in each laminate when 14 laminates were used. The composites made using a fine L-PLA powder were similar in nature to those made using 28

laminates. Again, because the polymer powder was dispersed throughout the reinforcing fibers, there was good contact between the polymer matrix and the reinforcing fibers. The resorbable composite plates prepared with solvent-bonded reinforcing fibers also had better mechanical properties than those prepared using heat and pressure alone. Because the fibers were in intimate contact with the matrix polymer before the layup procedure was begun, the final composite contained CMP fibers that were in good contact with the polymer matrix.

In addition to the fabrication improvements described above, we also incorporated some diagonal fibers into the composites to be implanted. This was done to help reduce the incidence of composite fracture along its longitudinal axis that had occurred in some of the previous implants while attaching the composite to the bone. We previously reported that four layers (of the total 14 layers) of $\pm 45°$ reinforcing fibers did not increase the torsional strength of composite plates and resulted in lower flexural properties. For this reason, we used only two layers of $\pm 30°$ fibers equally spaced in the composite to help reduce longitudinal fracture.

After the composites were fabricated, it was necessary to coat them with a continuous layer of PCL. However, we first had to cut the plates to their final 2-in. length and drill the holes for the bone screws. Because nicks and cuts in the outer coating (such as those created by drill holes) would expose fiber ends and allow fluid absorption, the coating had to be applied after the plates were cut and the holes were drilled. This meant that the coating process had to be able to coat the interior of the drill holes. Previously we had used a hot-film-coating technique, but this technique did not continuously coat recessed surfaces (such as drill holes). Therefore, we developed a fluidized-bed coating process so all of the exposed surfaces would be covered. This process involved dipping a warmed composite plate into a fluidized bed of the fine PCL particles, where the particles then clung to all surfaces of the composite. Once they were coated with powdered PCL, the samples were then placed in an oven to allow the PCL to completely melt. Once the coating completely melted, the PCL was allowed to recrystallize, and the screw holes that had been over-drilled were sized. These plates were then delivered to Dr. D.E. Bach USAIDR, who was to repair mandibular fractures in canines with these plates.

19. Evaluation of composite plates

Replicate plates were prepared by the method described in the previous section for testing in vitro. Our standard three-point bending evaluation was performed after one, two, and four weeks in 37 °C PBS. These composite plates were tested under three different configurations: uncoated and cut mini plates (1.5 x 0.25 x 0.125 in.), PCL-coated mini plates, and implant-size plates (2 x 0.5 x 0.125 in.) that had screw holes drilled before they were coated with PCL. We had previously shown that nicks and cuts such as drill holes provide a pathway for moisture to travel into the composite, which destroyed the fiber/polymer interface and rapidly weakened the composite plate. Therefore, the evaluation of these three groups of plates provided a complete degradation profile ranging from small plates that were severely cut to implant-size plates coated with PCL. It also allowed us to directly compare strength loss profiles in vitro to plates we had previously prepared and evaluated.

In Figures 53 and 54, we have illustrated the changes in average flexural modulus and strength of the coated mini and coated implant-size plates after incubation in 37 °C phosphate-buffered saline for zero, two, and four weeks. From these two figures, we see that the coated mini and implant-size plates initially weakened at similar rates. After four weeks in saline, the loss of flexural properties was practically the same (approximately 45%) for both groups.

The initial flexural properties of these uncoated mini plates were similar but greater than those obtained previously (Figures 44 and 45). This increase was probably due to the tedious fabrication procedures used to prepare the plates and occurred although there were two cross-ply laminates. The application of the PCL outer coating had little if any influence on the initial flexural properties. The primary difference in the response of flexural properties to incubation in saline of these two groups of plates (Figures 53 and 54 versus Figures 44 and 45) is the rate of flexural strength and modulus loss. As shown in Figures 44 and 45, the drop in the flexural properties of uncoated plates over a one- to two-week period can be up to 90% of the original values. This was not the case, however, with these PCL-coated plates. Over a four-week period in saline, the plates gradually weakened and became more compliant and retained greater than 50% of their flexural strength and modulus. This enhanced strength retention after incubation in saline was not due to the mechanical strength of the PCL, but rather was a result of its relatively low fluid transmission properties. Although the coating turned out to be thicker than we would have liked for it to be, the advantages it offers in protecting the plates from fluid infiltration are obvious when comparing the durability of coated versus uncoated plates.

The data in Figures 53 and 54 also compare the decay of flexural properties of replicate plates prepared like those supplied to USAIDR. The primary difference between the coated mini plates and coated implant-size plates were their size, and the implant-size plates had four drill holes. Stress calculations were based on the original dimensions of the plate but did not account for the change in cross-sectional area due to the drill holes. Thus, we expected that these drilled plates were somewhat weaker. Nevertheless, these studies showed that the plates to be used by USAIDR in the canine studies were strong and rigid and weakened at a rate commensurate with the bone's ability to heal and begin bearing loads.

20. Preparation of biodegradable bone-plate fixation screws

To prepare a totally resorbable fixation device, the attachment method must also be resorbable. In an effort to make our device totally resorbable we examined the use of resorbable fixation screws. Therefore, L-PLA rods, 5.6-mm diameter, were prepared and shipped to Dr. D. E. Bach, USAIDR, for machining into biodegradable bone screws. These screws were to be evaluated with some of the coated L-PLA plates during the studies with canine mandibles.

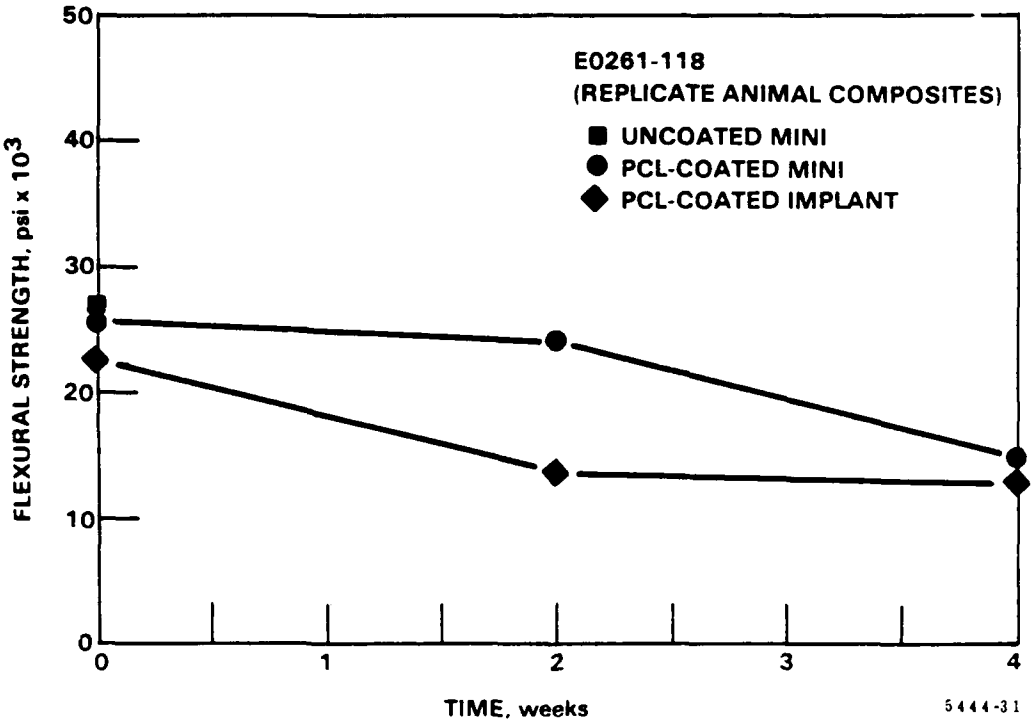


Figure 53. Loss of flexural strength of PCL-coated L-PLA composites after incubation in phosphate-buffered saline at 37 °C.

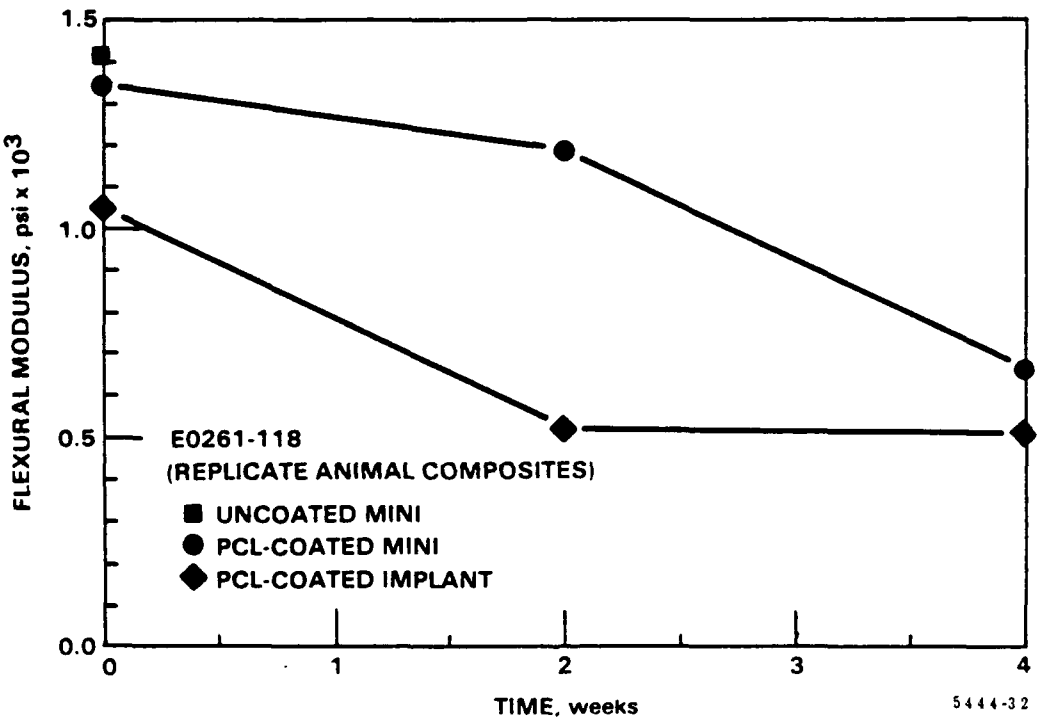


Figure 54. Loss of flexural modulus of PCL-coated L-PLA composites after incubation in phosphate-buffered saline at 37 °C.

IV. CONCLUSIONS AND RECOMMENDATIONS

The goal of this project was to develop a biodegradable material capable of withstanding loads equivalent to that of bone initially, and gradually lose its integrity. The result should be that as the bone heals, it sustains the increasing loads, leading to more rapid healing and the development of healthier bone. Initial attempts to prepare these plates from biodegradable polymers were unsuccessful due to low flexural properties. We discovered that reinforcing the polymers with fibers of nonbiodegradable ceramics provided the necessary strength and modulus. Attempts to prepare the plates from biodegradable ceramic fiber were unsuccessful because of the low strengths obtained from the poor fiber quality of the ceramic. Evaluation of biodegradable glass fiber as a reinforcing material proved to be the best choice. This calcium metaphosphate glass not only produced high quality and high strength fiber but resorbable bone plates reinforced with this fiber were produced with initial strengths and moduli greater than that of normal healthy bone. Unfortunately, when these composite plates were placed in a fluid environment (in vitro or in vivo), they lost their strength at a rate faster than the rate perceived to be required clinically. In our efforts to more fully understand the causes behind this rapid decline in mechanical strength, we found that the fluids diffusing into the composite through the biodegradable matrix itself or along exposed reinforcing fiber ends quickly destroyed the polymer/fiber interface. This resulted in a greatly weakened structure although there was minimal chemical degradation or mass loss. Because we felt the composite plates had adequate initial strengths, we turned our efforts toward examining ways to slow the rate of mechanical degradation without affecting the composite's initial strength and modulus. These investigations involved examining other biodegradable polymers as matrix materials, the use of commercial sizing agents and other materials as coatings for the reinforcing fibers and as outer coatings for the composite, and variations in the fabrication technique dictated by the selection of matrix polymer and reinforcing fibers. The composite system that showed the most promise consisted of a high-molecular-weight (high-MW) L-PLA matrix reinforced with 35% small-diameter CMP fibers and coated with a continuous layer of PCL.

High-MW L-PLA was chosen as the matrix polymer because it gave a steadier time/strength profile in saline than lower-MW L-PLA and other biodegradable polymers tested. This was probably due to the low fraction of amorphous material in the L-PLA, which is where moisture first enters the polymer. However, high-MW L-PLA also had relatively poor melt-viscosity flow properties, which made its use in the fabrication of composites difficult. This fact, coupled with the use of smaller-diamter CMP fibers, forced us to adopt a tedious and time-consuming composite fabrication process. Nonetheless, we chose to use high-MW L-PLA as the polymer matrix in the resorbable composite plates to be used to repair mandibular fractures in dogs because of its ability to protect the CMP fibers in a fluid environment.

We independently showed that composite fabrication techniques using either a greater number of thinner laminates, laminates containing solvent-bonded CMP fibers, or matrix polymer in the form of powder all improved the mechanical properties of resorbable composites. They also, to some degree, slowed the rate of mechanical degradation of composites that had been placed

in saline. The reasons for the improvement in strength and durability probably relate to superior contact between the polymer matrix and the reinforcing fibers. Because each of these three improvements independently improved the performance of composites, we incorporated them into the bone plate we prepared to be used by the Army for repairing mandibular fractures in dogs. In vitro analysis of replicate plates showed that sufficient strength and modulus were maintained for a period equivalent to that required for the bone to heal and begin bearing load. Although these studies were conducted in vitro, we believe that similar results would have been obtained in vivo.

We had planned to test and evaluate the retrieved biodegradable composite plates being used in the canine implant study and to complete modifications on our CMP fiber-drawing unit prior to the scheduled end of the contract. However, the plates were not implanted and therefore were not available for evaluation. The evaluation of retrieved biodegradable plates would have provided a comparison between the results of in vivo tests to our large data base of in vitro evaluations.

Our technical efforts on this project ceased as of April 21, 1988, the contract completion date. A proposal for the extension of this contract or the award of a new contract was submitted to the Army in 1987. This proposal described our proposed efforts to develop an improved biodegradable composite material using a new polymeric system. The primary deficiencies in our current technology were the inability of the fixation appliance to be conformed to the contour of the mandible at the time of surgery and the inherent strength-loss properties (due to water absorption) of the lactide matrix polymer. Successful completion of the proposed efforts would eliminate both of these problems. However, USAIDR has decided not to proceed with further research into this area.

V. ACKNOWLEDGEMENTS

We wish to acknowledge the Institute staff who had provided valuable assistance in completing the tasks undertaken during this project. Without their assistance, completion of the project would not have been possible. In particular, we wish to extend our thanks to Mr. David N. Ellis, Jr., Assistant Biomathematician, who performed much of the laboratory work reported here, and to the polymer division staff for their assistance in preparing the polymers used in this project.

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APPENDIX A

PATENTS

United States Patent [19]

Dunn et al.

[11] **Patent Number: 4,655,777**

[45] **Date of Patent: Apr. 7, 1987**

[54] **METHOD OF PRODUCING BIODEGRADABLE PROSTHESIS AND PRODUCTS THEREFROM**

[75] Inventors: **Richard L. Dunn; Robert A. Casper,** both of Birmingham, Ala.

[73] Assignee: **Southern Research Institute,** Birmingham, Ala.

[21] Appl. No.: **563,191**

[22] Filed: **Dec. 19, 1983**

[51] **Int. Cl.**[4] **A61F 1/00**

[52] **U.S. Cl.** ..... **623/16;** 623/17; 623/18; 623/19; 623/20; 623/21; 623/22; 623/23; 128/92 YQ

[58] **Field of Search** ..... 3/1, 1.9; 128/92 C, 128/92 G

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Primary Examiner—John Kight
Assistant Examiner—Kriellion Morgan
Attorney, Agent, or Firm—Needle & Rosenberg

[57] **ABSTRACT**

Method of producing biodegradable prostheses comprising a composite of resorbable fibers reinforcing a biodegradable polymer matrix and the use thereof in medical applications such as bone plates and other orthopedic devices. The fibers include ceramic powders, β-TCP and CaAl and a biodegradable glass, CMP.

11 Claims, No Drawings

METHOD OF PRODUCING BIODEGRADABLE PROSTHESIS AND PRODUCTS THEREFROM

The government has rights in this invention pursuant to contract DAMD17-78-8059 awarded by the U.S. Army Institute of Dental Research, U.S. Army Medical Research and Development Command.

BACKGROUND OF THE INVENTION

The need for improved methods and materials to manage severe maxillofacial injuries is well recognized. In such cases, the surgeon faces the dual problem of restoring function and appearance. The patient suffering from an extensive maxillofacial injury is typically confronted with disfigurement, impaired speech, and eating difficulties as well as the psychological trauma resulting from the injury.

Ideally, fixation applicances should maintain the fractured bone segments in close approximation for the promotion of primary union and healing, provide sufficient strength and rigidity to prevent disruption of the primary union by external forces, and as the union becomes further ossified, transfer an increasing proportion of the external load to the healing bone so that it will be strained and exercised. The fulfillment of these criteria is necessary for the formation of healthy, hard tissue that has properties commensurate with those of virgin bone.

Implant materials used for such injuries over the years belong to three traditional classes: metals, ceramics, and polymers. The choice of material for the particular application depends on the type and magnitude of applied loads which the implant is expected to experience in vivo and whether the implant is to be a permanent or a temporary augmentation. When trying to make repairs to the skeletal system, surgeons and engineers must attempt to replicate the static and dynamic responses of bone. Bone consists of a framework of collagenous fibers, a mineral matrix consisting primarily of calcium hydroxyapatite, and a small amount of polysaccharides. Although bone is stronger and less deformable than polymeric materials, it is weaker than metals. Historically, metals have received wide application for the construction of devices for fixing fractures. Metals exhibit high values of tensile strength and compressive modulus; they can be fabricated into fixation hardware by a variety of conventional techniques; and they provide excellent resistance to the in vivo environment. Metals and alloys now used as surgical implants include 316 stainless steel, several cobalt-chromium alloys, titanium, zirconium alloys and tantalum.

In mandibular fracture repair, one of the major disadvantages with metal implants is atrophy of the healing bone as a result of the stress-protection effect of the rigid metal plate. Other drawbacks with metal fixation appliances are that they may cause local inflamation and may corrode with age.

Among the metallic materials, tantalum is superior in resistance to corrosion and has been extensively employed as fixation plates for fractured bones and as implants. The metal is, however, difficult to process. In contrast, ceramic materials show good affinity to bones often with bone tissue penetrating into the fine pores of the ceramic to produce a strong fixation. Bone and tissue compatibility with ceramics is excellent. The main disadvantage of ceramic materials is their poor impact strength as they are often brittle. This condition is quite evident with the more porous ceramics and leads to poor durability of ceramic implants and fixation devices. On the other hand, polymeric materials provide excellent impact strength, good biocompatibility, and they are easily molded to the desired shape; however, they do not possess the required strength and stiffness for bone fixation.

Those materials and many of the prior art materials suffer from the common drawback of being permanent. In many applications, such as a fixation appliance holding a fracture together while it heals, it is highly desirable if the implant can be resorbed by the body. Such an implant would biodegrade over a period of weeks or years, and be gradually replaced by natural bone growth. Such materials eliminate the need for a second surgery to remove the implant. However, homogenous fixation plates previously fabricated from biodegradable polymers have been shown to possess insufficient strength and rigidity for initial fracture fixation. Porous resorbable ceramics have also been used in bone repair, but they must be used in conjunction with other support because of their fragile nature.

The prior art includes U.S. Pat. No. 3,929,971 which discloses a synthetic material (either hydroxapatite or whitlockite) that may be used with other materials, such as organic polymers, to form a composite substance which could be useful in constructing a degradable prosthetic implant; U.S. Pat. No. 3,905,047 which discloses a biodegradable prosthesis containing an eutectic or metal pyrophosphate and high-modulus fibers formed of a refractory metal oxide; U.S. Pat. No. 4,330,514 is directed to a process for preparing a hydroxyapatite ceramic which is used in a nondegradable implant comprising the ceramic and an organic binding material; and U.S. Pat. No. 4,356,572 which is directed to a porous biodegradable bone implant which utilizes calcium carbonate in crystalline form.

SUMMARY OF THE INVENTION

The disadvantages of the prior art are overcome by the present invention comprising biodegradable, high-strength, rigid fixation systems formed of composites of biodegradable polymers reinforced with resorbable fibers, particularly calcium phosphate fibers; the degradation products of the composites of the present invention are nontoxic and harmless to the host. The preferred polymers include polyglycolide (PGA), poly(DL-lactide) (DL-PLA), poly(DL-lactide-co-glycolide) (DL-PLG), poly(L-lactide) (L-PLA), poly(L-lactide-co-glycolide) (L-PLG), polycaprolactone (PCL), polydioxanone, polyesteramides, copolyoxalates and the polycarbonates because of their degradation times and their degree of control of degradation.

The reinforcing fibers include the ceramic or the preferred glass forms of calcium phosphate. The ceramic fibers include those comprising β-tricalcium phosphate. These fibers may be prepared by wet-spinning mixtures of the powders with different polymeric binders, such as polyacrylonitrite (PAN-A), and solvents, such as dimethyl sulfoxide (DMSO). Ceramic loading, oxidative pretreatment, coupling agents and sintering conditions affect spinnability and fiber properties. Fibers of phosphate-free calcium aluminate (CaAl) produced by the same process may also be used although the resulting fibers are fragile and may fracture easily.

Due to the highly porous and fragile nature of the fibers produced from the ceramic powders, the pre-

ferred fibers of the present invention are glass fibers. Smooth, uniform fibers of calcium metaphosphate [$Ca(PO_3)_2$](CMP), a bioabsorbable glass, may be prepared by extruding or pulling filaments from a melt and air quenching. Fibers can also be prepared by the same process from a partially bioabsorbable glass composed of a mixture of silicon dioxide, sodium oxide, calcium oxide and phosphorous pentoxide.

It is preferred to use continuous filament fibers so that a high ratio of length to cross sectional area is obtained, the length to diameter or aspect ratio ranging from 10:1 to 1,000,000:1.

DETAILED DESCRIPTION OF THE ILLUSTRATIVE EMBODIMENT

The present invention relates to the incorporation of high-strength, high-modulus, biodegradable fibers in biodegradable polymers to form totally absorbable fracture-fixation plates or devices. The use of two bioabsorbable ceramic powders, β-TCP and CaAl, and a bioabsorbable glass, CMP, is described.

(A.)

Preparation of Ceramic Materials

Bone contains a matrix of calcium hydroxyapatite, a resorbable ceramic material, in callagen. The calcium hydroxyapatite provides rigidity and the same material, when incorporated into biodegradable polymers, should provide the necessary reinforcement for use as fixation plates or devices. A variety of ceramic forms of hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$] and tricalcium phosphate [$CA_3(PO_4)_2$] have been reported in the literature. Recent evidence indicates that ceramic forms of hydroxyapatite are inert as implant materials while whose of tricalcium phosphate (Whitlockite) are bioabsorbable. The strength, durability, and absorption kinetics of tricalcium phosphate ceramics depend on the phasic nature of the final product, the lattice structure of the phases present, and the porosity and total surface area. Preparation of a calcium phosphate ceramic of high purity and single-phase nature is accomplished by the precipitation method of Salsbury and Doremus for production of β-Whitlockite (β-TCP), as follows:

A solution of calcium nitrate (1.40 moles) in 900 mL of distilled water is brought to pH 11 to 12 with concentrated ammonium hydroxide and thereafter diluted to 1800 mL. A solution of ammonium phosphate (1.00 moles) in 1500 mL distilled water is brought to pH 11 to 12 with concentrated ammonium hydroxide and thereafter diluted to 3200 mL to dissolve the resulting precipitate. The pH is again checked and additional concentrated ammonium hydroxide is added if necessary.

The calcium solution is vigorously stirred at room temperature, and the phosphate solution is added in drops over 30 to 40 minutes to produce a milky, somewhat gelatinous precipitate which is then stirred overnight (more than 12 hours). The reaction mixture is then centrifuged, and the clear supernatant fluid decanted. The resulting mineral sludge is homogeneously resuspended in distilled water to serve as a feedstock.

To produce green states which should afford 100% β-Whitlockite ceramics, aliquots of the feedstock are recentrifuged, homogeneously suspended in two volumes of dilute aqueous ammonium sulfate (1 to 2%) and then filtered on a Buchner funnel with application of mild suction and a rubber dam. After filtration for several hours, the compact clay-like cake is dried intact at 90° C. for 15 hours to produce directly the green state.

Sintering conditions, of course, may vary with the material and the phase or phases desired in the final product. For the production of β-Whitlockite, the green cake may be placed on an alumina dish and initially heated to 600° C. over 0.5 hours. The temperature is then raised quickly to 1150° C., the cake is sintered isothermally at 1150° C. for 1 hour, the temperature is reduced to 900° C., and the ceramic is cured at 900° C. for 4 hours.

Calcium aluminate is another resorbable ceramic material. Calcium aluminate of a 50:50 Ca/Al wt % composition [$CaAl_2O_4$] (CaAl) was 60% resorbed after one year implantation in monkeys. The Ca/Al ratio can be varied to produce several combinations of crystallographic phases and the various phases hydrolyze at varying rates providing a method for controlling the rate of ceramic dissolution. CaAl can be purchased from Pfaltz & Bauer, Inc., Samford, CT consisting of $CaAl_2O_4$ with quantities of Al_2O_3 and $Ca_{12}Al_{14}O_{22}$ as impurities.

(B.)

Preparation of Fine-Particle Sized Ceramic Powder

To prepare reinforcing ceramic fibers, especially with small diameters, it is necessary that the ceramic material consist of small particles. The small particles allow the extrusion of small-diameter ceramic filaments, and the finer particle size results in greater densification on sintering. Greater densification and the associated reduction in void volume of formed articles produces ceramic products, whether in pellet, rod or fiber form, with greater strength and structural rigidity. In addition, the breaking strength of sintered ceramic fibers is usually inversely proportional to the diameter of the fiber; thus, the smaller the fiber, the stronger it is per unit size. The same relationship has been found with sintered TCP fibers.

One method to reduce the ceramic powder to small particles is the use of a Megapack high-energy vibratory mill. The system employs the use of small-diameter steel balls vibrating at high frequencies for grinding of ceramic powders. The procedure used to grind ceramic samples to fine particle sizes with this mill is as follows: A slurry of TCP (or phosphate-free CaAl) in water was added to the vibratory mill, and the mill was activated and allowed to run for 4 hours. During that time, samples were taken at periodic intervals and examined by scanning electron microscopy (SEM) to determine particle-size range. A milling time of 4 hours was found to be sufficient to yield particles in the 1- to 2-μm range. At the end of that time, the slurry was removed from the mill and centrifuged for 30 minutes at 100 g. The supernatant was decanted and dimethyl acetamide was added to the centrifuge bottle; the contents were then agitated to resuspend the compacted ceramic powder. This process was repeated several times until all of the water was replaced by dimethyl acetamide.

The vibratory milling technique allowed preparation of slurries of ceramic powder in the appropriate polymer solvent both effectively and efficiently. Ceramic particles in this size range were appropriate for use in the wet-spinning of fine diameter filaments.

(C.)

Wet-Spinning of Ceramic Fibers Using Polymeric Binders

Of the number of methods for use in the production of ceramic fibers examined, fiber production by wet-spinning appears to be the most successful method. Simplistically speaking, fiber production by wet-spinning involves extruding a mixture of ceramic powder, binder (PAN-A), and solvent (DMSO) into a trough or bath containing a non-solvent for the binder. During extrusion into the non-solvent bath, the mixture coagulates to form a fiber or filament. For success in making fibers by wet spinning, the solvent for the binder must be soluble in the coagulating bath, which must be a non-solvent for the binder.

The fibers or filaments are subsequently drawn from the coagulating bath using a series of water-flushed, heated godets to rinse and evaporate the remaining solvent. After passing through the rinsing and drying system, the fibers are taken up on a winding reel. The collected fibers are then soaked in distilled water to assure complete solvent removal and are, thereafter, dried in an air-circulating oven to produce the final dried fiber. For the production of fibers from both β-TCP and phosphate-free CaAl, it is necessary to sinter the dried fibers in an inert atmosphere (nitrogen) maintained above 1150° C. to achieve coalesence and densification of the ceramic particles.

1. Polymeric Binders

As a consequence of the elevated temperature required for proper sintering of both β-TCP and phosphate-free CaAl, polymeric binders with superior thermal stability are required for use in the wet-spinning process. Although no resin yet produced is capable of withstanding these temperatures, three highly thermally stable resins were examined to see if they might effectively bind the ceramic powders together in fiber form until preliminary sintering (lower temperature) was achieved. These binders were Barex 210 (Vistron Corp., Chemicals Division, Cleveland, OH), a terpolymer mostly composed of acrylonitrile; Polyacrylonitrile Type A (PAN-A) (Du Pont, Wilmington, DE); and Ethocel #1 Standard (Dow Chemical Co., Midland, MI), an ethylcellulose material.

The thermal stability of PAN-A and, hence, the spun fiber, may be enhanced by subjecting the material to an oxidative pretreatment. The pretreatment improves thermal stability by forming a ladder polymer. Ethyl cellulose offered similar thermal stability without the necessity of a pretreatment step, although the fibers prepared with ethyl cellulose are inferior to those with PAN-A as a binder.

2. Dispersing agents

In wet spinning of ceramic fibers, dispersing agents are often used to prevent clumping of the ceramic particles and plugging of the in-line filter screen. Nuosperse, obtained from Tenneco Chemicals (Piscataway, NJ) is more compatible with the spinning solvent, DMSO, than Tamol 960 and Tamol SN from Rohm and Haas (Philadelphia, PA). It was successful in preventing clumping of the ceramic particles, and its addition to the spinning dope improved the spinnability of the ceramic materials.

3. β-TCP fibers

TCP powder prepared as described previously was wet sieved using No. 60 (250-μm) and No. 140 (160-μm) sieves. The fine particle cut was used to make the spinning dope. TCP was mixed with a solution of PAN-A in DMSO to make up the spinning composition. Care was taken to remove any entrapped air bubbles. The final spinning dope consisted of 7.4% TCP, 1.8% PAN-A, and 90.8% DMSO on a weight basis.

Fibers were prepared by wet extrusion using a hypodermic syringe and hypodermic needles of various sizes. The needles ranged from 15 G (1.37 mm ID) to 27 G (0.2 mm ID). Distilled water at room temperature was used as the coagulating medium. The spinning dope was loaded into the syringe barrel, and the tip of the needle was placed below the surface of the coagulating fluid. Pressure was applied until a bead of coagulum formed at the needle's tip. The bead was grasped with a pair of tweezers and pressure was reapplied to the syringe barrel. Fibers were extruded for the length of the coagulating bath. Fibers prepared using the smaller diameter needles were considerably more difficult to extrude than fibers prepared using the larger needles. The extruded fibers were removed from the coagulating bath and placed in another water bath and allowed to soak to remove solvent. After soaking for a sufficient time, the fibers were removed from the bath with tweezers and placed on Teflon sheeting to dry in air overnight. The smaller fibers were easier to handle and exhibited more structural integrity. This was probably due to a higher residual solvent content in the larger fibers.

β-TCP fibers were also prepared on wet-spinning equipment designed for production of rayon fibers. A spinning dope consisting of 10% β-TCP, 15% Barex 210 acrylic polymer, and 75% N,N-dimethylacetamide was loaded into a cylindrical, stainless steel feed pot. The feed pot was pressurized with compressed air (20 psi), and the spinning dope was forced from the feed pot through stainless steel tubing (0.25-in.-OD, type 304) to a Zenith gear pump driven by a Zenith Model QM drive motor. The Zenith pump delivered the spinning dope (at 0.29 cm^3 per revolution; 1.45 cm^3/min) to a spinneret with an orafice diameter of 0.020 in. The spinneret was submerged in a water bath. As the spinning dope came in contact with the water, it coagulated to form a fiber. After traversing the coagulation bath (18 in.), the fiber was taken up by the first godet. This godet (80 ft/min surface speed; 107° F.) was equipped with a tap water spray to remove solvent from the fiber. The fiber was then taken up on a second heated godet (84 ft/min surface speed; 97° F.) and rinsed with a warm water spray. The fiber was passed around a third heated godet (87 ft/min surface speed; 105° F.) and collected on a Leesona Model 955 take-up winder.

The fibers were then subjected to oxidative pretreatment to promote the formation of a ladder polymer and enhance the thermal stability of the binder matrix. Pretreatment was accomplished by placing the fibers in an air-circulating oven maintained at 200° C. for 30 minutes. Pyrex test tubes were used to contain the fibers during the pretreatment process. The fibers changed from white to tan during pretreatment.

After pretreatment, the fibers were sintered in a Lindberg Hevi-Duty SB oven. The oven was maintained at 1200° C. and purged with nitrogen for the duration of the sintering cycle. The sintered fibers were light yellow. After sintering, some of the fibers shrank to less than 40% of their original diameter.

The fibers were tested for breaking strength on an Instron Model TMS Serial 72 testing machine. The fibers were prepared for testing by mounting on card-

board tabs. The finest fibers were attached to the tabs with paraffin, and the larger fibers were attached with sealing wax. Samples were pulled at a rate of 1 in./min. until fracture occurred and the force at break was determined. After being tested, the samples were removed from the Instron, the diameter at the fracture point was determined with a micrometer and used to calculate the breaking strength in terms of force per unit area. The fracture surfaces were then examined by SEM. The test results are presented in the following table:

BREAKING STRENGTH OF TRICALCIUM PHOSPHATE FIBERS

Average diameter mm	Breaking strength psi
0.559	169
0.508	353
0.356	69
0.124	419
0.122	477
0.074	1607

There is a dramatic effect of fiber diameter on tensile strength. As fiber diameter decreases, the strength increases. Such behavior is commonly found in the preparation of ceramic fibers. Results shown in the table reflect the average of test results for five specimens of each fiber diameter. One sample of the smallest diameter fiber had a tensile strength of 2500 psi. SEM photos showed voids and irregularities at the fracture surface of all specimens. In general, larger voids were associated with lower breaking strength, reflecting the stress-concentrating effects of the irregularities.

4. CaAl fibers

Fibers of phosphate-free calcium aluminate were prepared following the procedures used for β-TCP fiber production and using the same solvent and binder. After sintering, the fibers were quite fragile.

Calcium aluminate (Pfaltz & Bauer, Inc., Stamford, CT) was used to prepare the fibers. X-ray diffraction analysis revealed that the powder consisted of $CaAl_2O_4$ but also contained significant amounts of Al_2O_3 and $Ca_{12}Al_{14}O_{22}$. The CaAl was dry sieved through a No. 100 sieve (150-μm) to break up any clumps and remove any large particles.

The spinning dope had a ceramic-to-binder ratio of 80:20 and consisted by weight of 25% CaAl, 6% PAN-A, and 69% DMSO. Fibers were extruded from a hypodermic syringe and needle, as were the TCP fibers. Needle sizes 15 G through 25 G were used to form fibers. The 27 G needle proved to be too fine for the CaAl dope. The fibers were coagulated in a tap-water bath at ambient temperatures. The coagulated fibers were quite rigid and easier to handle than the TCP fibers at this stage. CaAl fibers were also prepared by the pilot-scale equipment used for the β-TCP fiber production. A 70:30 by wt blend of CaAl and Barex 210 in a suspension in N,N-dimethylacetamide was extruded at a rate of 1.75 cm^3/min into tap water at 70° F. The first and second godets were operating at a speed of 94 ft/min and the third godet at a speed of 96 ft/min. The temperatures were 110°, 115°, and 115° F. for the three godets respectively. The fibers were dried at ambient conditions overnight. Oxidative pretreatment was performed in a circulating-air oven at 200° C. for 30 minutes. Prior to oxidation the fibers were white. After oxidation the fibers turned brown. The fibers were then placed in an oven under a nitrogen purge, heated at 1200° C., held for 1 hour, and allowed to cool overnight. When the fibers were removed from the oven, they were found to be extremely fragile.

(D.)

Fiber Production From Biodegradable Glasses

Although sintering of ceramic particles produces bioabsorbable ceramic fibers, the voids still present in the fibers cause them to be somewhat fragile and weak. A void-free ceramic fiber produced by melting and extrusion of a bioabsorbable glass gives a stronger and more durable fiber for use in polymer reinforcement. Glasses are converted to fibers by drawing fibers from hot melts. The high surface tension and slow rate of change of viscosity with temperature of melted glass permits formation of stable meniscuses and enables fibers to be formed and drawn from a suitable crucible after the natural flow of molten glass downward by gravity. Both marble melt and direct melt processes are used to produce glass fibers.

1. Bioglass fibers

Bioglass is a partially biodegradable glass composed of 45% silicon dioxide, and various metallic oxides (sodium oxide, calcium oxide and phosphorous pentoxide). Only the silicon dioxide portion of the glass is non-absorbable.

Fibers were prepared from the Bioglass by heating the material in a crucible until it became molten (900° C.) and withdrawing filaments with a stainless steel rod. Fibers were produced by this procedure, but there was considerable variation in both fiber diameter from sample to sample and uniformity of diameter throughout the length of a given sample. Samples of the glass fibers were mounted and tested in the same manner as the ceramic fibers. Breaking strength of the glass fibers varied from 9000 to 50,000 psi. This variation was to be expected in view of the lack of uniformity from one sample to the next. However, the formation of fibers with high tensile strengths was evident.

Fibers prepared in the fashion described above were tested for bioabsorption. Samples of the fibers were cut into 2-in. lengths for breaking-strength determination, and the 2-in. lengths were weighed. Some fibers were mounted and broken to determine initial breaking strength. Their average initial breaking strength was about 45 000 psi, and their average diameter was 0.026 mm. The remaining fibers were placed in phosphate-buffered saline at a pH of 7.2 in a 37° C. oven for 18 days. The fibers were then removed from the saline, dried, reweighed, and broken to determine final breaking strength. Their average weight loss was about 5%, and their average breaking strength was less than 200 psi.

2. CMP fibers

CMP is known as a hydrolytically unstable glass. Consisting of calcium and phosphorous, it degrades within the body to harmless components of normal body fluid. CMP, however, must be properly purified before it can be spun into fibers for use in reinforcing biodegradable polymers. Following the procedure given in U.S. Pat. No. 4,049,779, CMP of sufficient purity for fiber formation is obtained. One liter of a 3-molar solution of phosphoric acid was prepared. One hundred grams of $CaCo_3$ was then slowly dissolved in the acid solution. Impurities were removed by precipitating with 2.5 g of ammonium 1-pyrrolidine dithiocarbamate dissolved in 50 mL of water. The resulting grey

precipitate was then removed by filtration. The supernatant was concentrated by evaporation, and the pure CMP was precipitated. The precipitate was filtered and washed with acetone to remove any residual phosphoric acid. The white material was then placed in an alumina dish and baked in an oven at 600° C. for 24 hours, 800° C. for 72 hours, and cooled slowly to room temperature. The baking steps allow the CMP salt to be chemically condensed and polymerized to produce the CMP glass.

The resulting grey, foamed, brick-like substance is then placed in an alumina or platinum crucible, heated in an oven at 600° C. for 2 hours, at 800° C. for 16 hours, and at 1000° C. for 2 hours, after which time the crucible is removed from the oven and transferred to the fiber-drawing apparatus. This equipment consists of an oxygen/natural gas heating source for the crucible and a 3.75 in. -OD stainless steel take-up spool for drawing the fibers. The speed of the spool can be controlled to produce fibers with the desired diameters. A typical draw speed of 7.2 in./sec. is used. The spool is also heated with a natural gas flame. By inserting the tip of a stainless steel rod into the molten glass, a fiber can be drawn from the melt and passed around the take-up spool. If the melt is maintained at the proper temperature (≃1000° C.), a very fine glass fiber can be wound on the take-up spool. The resulting fibers have good strength and uniformity. A typical fiber has a tensile strength of approximately 51,000–110,000 psi, an initial modulus of 5×10^6 psi, a diameter of about 5 mils, and a density of 2.67 g/cm^3. These properties are comparable to commercial glass fibers.

In vitro studies of the CMP fibers in 0.9% USP saline at 37° C. show the fiber begins to dissolve from the surface after only 10 days, and they are completely dissolved after 30 days.

(D.)

Biodegradable Composites

For the high-strength, high-modulus, bioabsorbable ceramic or glass fibers to be useful, they must be incorporated into a biodegradable polymer matrix. The matrix protects the fibers from abrasion and breakage, and they provide a structure for bone-fixation plates. The fibers in return provide the structural rigidity needed for the polymer plate or device to maintain support.

1. Biodegradable Polymers

The following polymers (with their approximate degradation times) are all candidates for the biodegradable composite of the present invention. These polymers are all biodegradable to water-soluble, nontoxic materials which can be eliminated from the body. All are well known for use in humans and their safety has been demonstrated and approved by the FDA. Although these polymers are normally linear, crosslinked resins can be prepared from these materials by those skilled in the art, and these materials are also included as suitable biodegradable polymer matrices.

Polymer	Degradation Time, Months
Polycaprolactone	24–36
Poly(L-lactide)	24
Poly(DL-lactide)	12–18
Polyglycolide	3–4
95:5 Poly(DL-lactide-co-glycolide)	12
90:10 Poly(DL-lactide-co-glycolide)	10
85:15 Poly(DL-lactide-co-glycolide)	9
75:25 Poly(DL-lactide-co-glycolide)	5
50:50 Poly(DL-lactide-co-glycolide)	2
90:10 Poly(DL-lactide-co-caprolactone)	9
75:25 Poly(DL-lactide-co-caprolactone)	6
50:50 Poly(DL-lactide-co-caprolactone)	2
Polydioxanone	12
Polyesteramides	4–12
Copolyoxalates	4–12
Polycarbonates	2–12
Poly(glutamic-co-leucine)	24–48

The preferred polymers are the poly(DL-lactide-co-glycolide) materials because of the degradation times and their degree of control of degradation. The poly(L-lactide-co-glycolide) materials not mentioned in the table should give similar results. Poly(DL-lactide) is also preferred as are the polydioxanone, polyesteramides, copolyoxalates and the polycarbonates. Polycaprolactone, poly(L-lactide), and the poly(glutamic-co-leucine) are less preferred because of their long degradation times.

With a composite formed from a biodegradable polymer and resorbable fibers, the strength decreases with resorption time within the body. This decrease in strength is important because the fixation plate transfers the load with time to the healing bone and prevents stress protection atrophy. The loss of strength of the polymer plates reinforced with biodegradable fibers will depend primarily upon the degradation rate of the polymer because the polymer completely encases the fibers. The degradation rate of the polymeric matrix depends upon the type of polymer used. It should be noted that the degradation times set forth above are for complete disappearance from the polymer. The time for strength loss in the composite will be considerably less and can be approximated as one half the total polymer degradation time. Composites which lose their strength in one month will be useful as well as those that last up to about one year. The preferred times will be three to six months. It should also be noted that the biodegradation times of the polymers and the corresponding strength losses of the composites will depend upon polymer molecular weights. The values given in the table are for normal molecular weights. Higher molecular weight polymers will last longer and those lower in molecular weight will degrade faster. The degradation rate of the polymer can be changed by control of molecular weight, by the type of biodegradable polymer, and by controlling the ratio of lactide to glycolide in copolymers.

2. Reinforcing Fibers

The term "fiber" as used herein is defined as any material that has a high ratio of length to cross sectional area with minimums suggested as 10:1 to 100:1, and a maximum cross sectional area of 7.85×10^{-5} in.^{2} and a maximum transverse dimension of 0.010 in. With continuous filament fibers which are preferred, the length to diameter (aspect ratio) is maximized to give the best reinforcement. However, the composites can be made with chopped or shorter lengths of fibers. With these, the aspect ratio is lower and the level of reinforcement is less. Thus, the aspect ratio can range from 10:1 up to really high numbers such as 1,000,000:1. The preferred range is 100:1 to 1,000,000:1.

3. Composite Fabrication

The fibers can be incorporated into the polymer matrices by several methods. In one approach, the fibers can be chopped into small pieces, mixed with the molten polymer, and formed into the desired shape by injection molding, compression molding, or extrusion. In another procedure, the chopped fibers can be mixed with a solution of the polymer and the mixture cast into a film with evaporation of the solvent. The films can then be laminated or molded to the desired shape. The preferred method, however, is to use continuous filaments of the fiber to provide maximum strength and regidity. Therefore, the ceramic or glass fibers are wrapped around a Mylar- or Teflon-coated mandril and dipped into or sprayed with a solution of the polymer in a suitable solvent. The solvent is evaporated, and the dipping or spraying repeated to obtain a composite film of the desired thickness. The film is then removed from the mandril, and pressed under pressure and heat to provide flat, bubble-free sheets. These sheets are then laminated with other sheets of the same composition or with polymer sheets containing no fibers to produce the fixation plate.

As an example, films of DL-PLA were prepared from purified polymers having inherent viscosities from 0.58 dL/g to 1.27 dL/g measured in chloroform at 30° C. Either ceramic or glass fibers are wrapped around a Mylar-coated mandril and sprayed with a solution of the same DL-PLA in p-dioxane. After the solvent evaporates, the spraying is then repeated to obtain a composite film of the desired thickness. When the appropriate thickness is obtained, the film is removed from the mandril, cut, and pressed with a hydraulic press maintained at 70° C. and 29,000 psi to provide flat, bubble-free sheets. These sheets are then laminated with sheets of the same polymer containing no fibers to produce a plate. Five sheets of fiber-reinforced material are combined with four sheets of polymer.

In another procedure, a hot-pressed film of PLA is placed in a mold and the film is brushed with solvent until it is tacky. Then a layer of the CMP fiber is placed lengthwise along the film taking care not to overlap the fibers which causes breakage. Additional solvent is then brushed over the fiber and another polymer film is placed over the fibers to which it readily adheres. The top of the new film is then wetted, more CMP fibers placed onto it, and the process repeated until 6 layers of fiber are laminated between 7 layers of film to give a composite with 40% by volume of CMP fiber. The solvent is allowed to dry completely, and the laminate is heat-pressed at 60° C. and 20,000 psi for 15 minutes. This gives better lamination of the films and removes any residual solvent bubbles.

The plates produced by this procedure were evaluated in three-point bending tests (ASTM D790). Flexural strengths of 6,000–10,000 psi and flexural moduli of about 1×10^6 psi were found. These compare favorably with those values obtained for nonbiodegradable polymer/fiber composites, and they show the improvements over non-reinforced biodegradable polymer plates.

Materials	Flexural Strength, psi	Flexural Modulus, psi
Bone	10,000–20,000	1 to 3 $\times 10^6$
Steel	75,000	30 $\times 10^6$
DL-PLA	2,000–4,000	0.3 $\times 10^6$
Carbon-reinforced DL-PLA	20,000–40,000	1 to 4 $\times 10^6$
CMP-reinforced DL-PLA	6,000–10,000	1 $\times 10^6$

4. Solvents for Biodegradable Polymers

The following table sets forth what solven:(s) will dissolve the biodegradable polymers useful in the present invention:

Polymers	Solvent
Polycaprolactone	dichloromethane,
90:10 poly(DL-lactide-co-caprolactone)	chloroform, toluene
75:25 poly(DL-lactide-co-caprolactone)	xylene, p-dioxane, and
50:50 poly(DL-lactide-co-caprolactone)	THF.
poly(DL-lactide)	
95:5 poly(DL-lactide-co-glycolide)	
90:10 poly(DL-lactide-co-glycolide)	
85:15 poly(DL-lactide-co-glycolide)	
50:50 poly(DL-lactide-co-glycolide)	HFIP (hexafluoroispropanol) and HFASH (hexafluoroacetone-sesquihydrate)
polydixanone	tetrachloroethane and chloroform
polyesteramides	cresol
copolyoxalates	chloroform
polycarbonates	ketones, esters and partially chlorinated hydrocarbons
poly(glutamic-co-leucine)	benzene

What we claim is:

1. A method of producing a totally biodegradable prosthesis or implant comprising the steps of

(a) encasing an effective amount of fibers selected from the group consisting of calcium phosphate, and calcium aluminate in a matrix of a polymer selected from the group consisting of polyglycolide, poly(DL-lactide), poly(L-lactide), polycaprolactone, polydioxanone, polyesteramides, copolyoxalates, polycarbonate, poly(glutamic-co-leucine) and blends, copolymers and terpolymers thereof to form a composite; and

(b) forming said composite to the desired shape.

2. A method as defined in claim 1 wherein said calcium phosphate fibers are comprised of β-tricalcium phosphate.

3. A method as defined in claim 1 wherein said calcium phosphate fibers are comprised of calcium metaphosphate.

4. A method a defined in claim 1 wherein said effective amount ranges from 10–90% by volume.

5. A method as defined in claim 1 wherein said effective amount is preferably 30–80% by volume.

6. A method as defined in claim 1 wherein the aspect ratio of said fibers ranges from 10:1 to 1,000,000:1.

7. A biodegradable prosthesis or implant, comprising

(a) a matrix formed from a polymer selected from the group consisting of polyglycolide, poly(DL-lactide), poly(L-lactide), polycaprolactone, polydioxanone, polyesteramides, copolyoxalates, polycarbonate, poly(glutamic-co-leucine) and blends, copolymers and terpolymers thereof; and

(b) fibers selected from the group consisting of calcium phosphate and calcium aluminate incorporated within said matrix in an amount ranging from

10–90% by volume and said fibers having an aspect ratio of 10:1 to 1,000,000:1.

8. A biodegradable prosthesis or implant as defined in claim 7 wherein said matrix is a film of said polymer and said prosthesis or implant comprises a predetermined number of alternating layers of said film and said fibers.

9. A method of repairing fractured bone segments in animals, comprising the step of surgically implanting adjacent said bone segments a prosthesis or implant formed of a composite of fibers selected from the group consisting of calcium phosphate and calcium aluminate, said fibers reinforcing a matrix formed from a polymer selected from the group consisting of polyglycolide, poly(DL-lactide), poly(L-lactide), polycaprolactone, polydioxanone, polyesteramides, copolyoxalates, polycarbonate, poly(glutamic-co-leucine) and blends, copolymers and terpolymers thereof.

10. A method of producing a totally biodegradable composite material for prosthetic and implant devices, comprising the step of encasing an effective amount of a reinforcing material in the form of fibers selected from the group consisting of calcium phosphate and calcium aluminate in a matrix of a polymer selected from the group consisting of polyglycolide, poly(DL-lactide), poly(L-lactide), polycaprolactone, polydioxanone, polyesteramides, copolyoxalates, polycarbonate, poly(glutamic-co-leucine) and blends, copolymers and terpolymers thereof.

11. A totally biodegradable composite material for prosthetic and implant devices, comprising:

(a) from 10–90% by volume of a reinforcing material in the form of fibers selected from the group consisting of calcium phosphate and calcium aluminate; and

(b) a polymer encasing said reinforcing material, said polymer being selected from the group consisting of polyglycolide, poly(DL-lactide), poly(L-lactide), polycaprolactone, polydioxanone, polyesteramides, copolyoxalates, polycarbonate, poly(glutamic-co-leucine) and blends, copolymers and terpolymers thereof.

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United States Patent [19]

Ropp

[11] **4,126,665**

[45] * **Nov. 21, 1978**

[54] **PREPARATION OF POLYMERIC ALKALINE EARTH METAPHOSPHATE GLASSES**

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[*] Notice: The portion of the term of this patent subsequent to Sep. 20, 1994, has been disclaimed.

[21] Appl. No.: **694,752**

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[52] U.S. Cl. ..... **423/314**; 423/305; 106/47 R

[58] Field of Search ..... 423/305, 309, 313, 314, 423/315; 106/47 R, 47 P, 47 B; 23/300, 305 R, 305 A, 305 F

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[57] **ABSTRACT**

Polymeric metaphosphate glasses, $[M(PO_3)_b]_n$, having chemical durabilities at least 40–400 times greater than those of the prior art are provided. In the formula, M is selected from the group consisting of Al, Be, Mg, Ca, Sr, Ba, Cd and Zn, and "*b*" has a value of 3 for Al and 2 for the other cations. The high durabilities of the glasses are achieved by controlled preparation of the precursor compounds in specific stoichiometric proportion, by heating the precursors in a controlled thermal cycle to induce preliminary polymerization of the intermediates, by thereafter melting said intermediates, and by subsequently holding said melt for a time to complete the polymerization. The melt is then cast to form the glass which is then annealed in the normal manner.

The disclosure involves in particular single high purity compound precursors which form single phase glasses. Each system is subject to mutual phase separation if mixtures are used; even impurities become segregated because each single-phase-glass system rejects said impurities during polymerization. Single phases are necessary because mixtures of glass phases are found to be less stable than the single phase glass of the present invention and cannot be prepared free from striae for use in optical or other applications.

12 Claims, No Drawings

PREPARATION OF POLYMERIC ALKALINE EARTH METAPHOSPHATE GLASSES

CROSS REFERENCE TO RELATED APPLICATION

The present application is related to subject matter disclosed in my prior copending applications Ser. No. 633,776, filed Nov. 20, 1975 now abandoned, entitled "Glasses Prepared by the Melting of Stoichiometric Compounds"; and Ser. No. 644,270, filed Dec. 24, 1975, entitled "Crystalline Salt Monomers for Stable Phosphate Glasses" now U.S. Pat. No. 4,049,779.

BACKGROUND OF THE INVENTION

Attempts to make phosphate glasses in a chemically stable form by methods employed in the prior art have been largely unsuccessful. Typical of such prior art systems in which phosphates are employed are those processes set forth in U.S. Pat. Nos. 2,434,281; 2,031,579; 2,064,344 and 3,485,646. The compositions utilized in those patents include P_2O_5 or H_3PO_4 or HPO_3. Compounds which decompose to the oxide to form a compound such as $NaPO_3$ and $Al(PO_3)_3$ have also been prepared from HPO_3 which are then used to prepare the glass. However, the prior art techniques do not recognize the criticality in obtaining a glass product of desired properties by preparing precursor compounds, to be melted to form the glass, in essentially pure stoichiometric monobasic form prior to melting the compounds. Also, no known prior art system appears to recognize the criticality of reacting the precursor monobasic compounds in a thermal process to obtain a melt which is further reacted to form stable phosphate glasses when appropriately cast and annealed. Moreover, there is no recognition in the prior art of the importance of restricting the glass composition to a single phase in order to achieve complete polymerization with consequent high resistance to hydrolysis in boiling water.

SUMMARY OF THE INVENTION

In accordance with the invention, phosphate glasses are obtained by first preparing monobasic phosphate precursor compounds of stoichiometric equivalent substantially free of phosphoric acid and impurities and then using these precursors to form the melt for the desired glass. The precursor compounds within the scope of the invention are represented by the formula:

$$M(H_2PO_4)_b$$

where M is a single metal selected from the group consisting of Al, Be, Mg, Ca, Sr, Ba, Cd and Zn and where "*b*" is 3 for Al and 2 for the other cations. Depending on the particular precursor, it may , or may not, contain waters of hydration.

In the preparation of the precursors of the invention a recrystallization from solution is employed both to obtain purification and high crystallinity. The reagent of choice in the preparation of these salts is H_3PO_4. The cation, in the form of oxide, hydroxide, or carbonate, is dissolved in dilute H_3PO_4. Once dissolution is obtained, the solution is purified by suitable means such as precipitation of impurities by the addition of organic complexing agents including ammonium 1-pyrrolidinedithiocarbamate. A suitable alternate is cupferron. The solution is filtered and further purified by mercury-pool electrolysis. The solution is then evaporated to obtain monomer crystals. These crystals are then washed thoroughly in acetone to remove all traces of phosphoric acid and are then dried. The crystals are then placed in a furnace and heated to cause initial polymerization and to form a melt. The heating process must be continuous and cannot be interrupted at any point before or afte. the melt has formed. The melt is maintained at a tem, erature about 100° C. over the minimum temperature required to form the melt e.g., for calcium the temperature is 1050° C.; for magnesium, it is 1200° C. The melt is held for a time to ensure complete polymerization, usually in the order of about 96 hours to about 120 hours. Longer times are not destructive to the melt but neither are they productive. At the end of the hold-time, the melt is then cast and annealed. For optical quality glass, the melt must be stirred to ensure homogeneity, e.g., stirring by helium gas bubbling is a suitable method. The melt must then be cast in a hot mold to obtain glass completely free from striae.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

One of the major properties adversely affecting the commerical usage of the non-silicate glasses is chemical durability. Chemical durability of a glass is usually defined in terms of the rate of chemical etching of the surface by a liquid such as boiling water. A convenient reference is the durability or weight loss of plate glass (soda lime silicate) in boiling water which is 0.053 $mg/cm^2/hr$. I have discovered, for example, that phosphate glasses prepared according to the present invention exhibit marked improvement in chemical durability and rival those of the silicate-based glasses. This is a highly significant order of change in the chemical durability of phosphate glasses which has not been achieved heretofore. For example, the prior art quotes durabilities for phosphate glasses ranging from 2.2 to 83 $mg/cm^2/hr$. For a calcium phosphate glass prepared according to the invention, I have achieved a durability of 0.11 $mg/cm^2/hr$ while an aluminum phosphate glass prepared according to the invention showed a durability of 0.000054 $mg/cm^2/hr$. Magnesium phosphate glass exhibits a durability of 0.084 $mg/cm^2/hr$. Strontium phosphate glass shows a durability of 0.23 $mg/cm^2/hr$ whereas barium phosphate glass has a chemical durability of 0.093 $mg/cm^2/hr$. These values are improved generally in the order of at least forty to as much as a thousand times over the durabilities of the prior art.

In accordance with the invention I have found that, for non-silicate glasses such as those based upon phosphates, it is desirable to form a stoichiometric compound, i.e. a precursor of specific proportions, which substantially freed of phosphoric acid and impurities and then used to form the melt to produce the desired glass. The resulting glass thereby exhibits properties not normally found for similar glasses of melts prepared otherwise. Glass thus prepared is useful in a variety of applications such as face plates for electronic display devices, as fiber optics, as optical lenses and other optical pieces and the like.

It must be appreciated that a chemically durable phosphate glass can only be achieved by limiting the glass composition to a single phase. Su. ', glass composition may be described by the metaphosphate formula:

$$[M(PO_3)_a]_n$$

where M is a cation selected from the group consisting of Al, Be, Mg, Ca, Sr, Ba, Cd and Zn, "n" denotes a degree of polymerization and has a value of at least 4 and "b" has a value of 3 for Al and 2 for the other cations. In nearly all cases in the prior art it is common to make various mixtures of cations in order to improve the chemical durability of the obtained glass. However, such prior art durabilities do not approach the durabilities achieved in the present invention.

I have found that a melt-rejection mechanism is present during the polymerization stages of the melt and that each specific composition, such as $[Ca(PO_3)_2]_n$ or $[Mg(PO_3)_2]_n$, form melts which are mutually exclusive so that separate glass phases result at the end of the polymerization process. This results in phase-separated glass with internal striae present. Glass with such striae is not useful in optical applications. I have further discovered that any impurities present in the glass melt become segregated and consequently become major contributors to a product lacking in chemical durability. When such impurities are present it is found that hydrolysis occurs at the points where the impurities are localized although the base glass itself does not appear to be attacked appreciably by the hydrolytic etching.

I have further determined that the most durable glass is that one which is exactly stoichiometric as the metaphosphate composition. This result appears to be specifically contrary to prior art wherein it is considered that the metaphosphate composition is the least stable; those with excess phosphate or with excess metal cation being considered appreciably more stable to hydrolysis etching than the metaphosphate composition itself. Thus, it appears that the factors which contribute to the unique high chemical durabilities (extremely low hydrolysis etching) found for glasses of the present invention are:

1. the use of a single phase glass composition,
2. obtaining a high degree of purity in the salt precursor to minimize impurity segregation in the melt with consequent increased resistance to hydrolysis etching,
3. maintaining the melt composition exactly at the metaphosphate formulation,
4. choosing a proper crucible material to hold the melt,
5. preheating the salt precursor in a controlled manner to initiate polymerization prior to melting,
6. continued heating to form a melt,
7. holding the melt for a time sufficient to complete the polymerization of the melt (usually about 96 to about 120 hours), and
8. casting the melt in a heated mold (300° ± 10° C. in graphite or lava, 110° ± 10° C. in stainless steel) if an optical quality glass is desired.

The glass casting is then annealed according to a predetermined annealing program. The melt must be stirred to obtain optical quality glass. Bubbling helium gas, or oxygen gas, through the melt is a suitable method. However, air or nitrogen should be avoided because I have found that such bubbles introduced into the melt cannot be easily dispersed. Also, reducing atmospherees degrade the melt and the resulting glass is less stable to hydrolytic etching by boiling water. The present invention is essence utilizes a single selected precursor compound of stoichiometric proportion which is melted to form a glass. Such precursors consistent with the invention are those having the formula:

$$M(H_2PO_4)_n$$

wherein M is one of the metal ions selected from the group consisting of Al, Zn, Cd, and the alkaline earth metals Be, Mg, Ca, Sr and Ba and wherein n has a value of 2 or 3 depending on whether M is a divalent or trivalent ion. Furthermore, the metal monobasic phosphate selected from this group must be purified to remove the impurity metal ions to a purity level superior to reagent grade of 5000–9000 ppm and preferably having no more than about 100 ppm total impurities. Impurity metal ions include metals other than M given above such as alkali metal ions e.g., Na, K, Li, the transition metal ions, e.g., Fe, Co, Ni, Cr, V, etc. and the so-called heavy metal ions, e.g., N, Mo, Ta, Au, etc.

A suitable method of purification is as follows. The selected cation as the carbonate, MCO_3, or the hydroxide, $M(OH)_2$, is dissolved in a controlled excess of H_3PO_4. The resulting solution is suitably filtered such as through a 0.45 micron filter to remove particulate impurities. Ten grams of suitable pecipitant, e.g., ammonium 1-pyrrolidinedithio-carbamate (APC) are weighed out dissolved in 50 ml of water, and added to about 4 liters of the solution. A precipitate forms which is removed by filtration through the 0.45 micron filter.

The steps in the preparation of a typical compound suitable for preparing a phosphate glass of improved properties over those of the prior art, in accordance with the invention, are set forth in my copending application, Ser. No. 644,270, filed Dec. 24, 1975. Once the salt precursor has been obtained, it will still contain small quantities of H_3PO_4. I have determined that even a very small fraction of H_3PO_4 present in the salt precursor changes the solid state reactions which occur and the resulting glass is measurably less stable to hydrolysis etching than a glass made from a pure, dry salt precursor. The desired salt precursor is exactly stoichiometric when prepared according to the method of the invention detailed in said copending application Ser. No. 644,270. The salt precursor reacts to produce an exactly stoichiometric metaphosphate melt. But if H_3PO_4 is present as a minor phase, it becomes incorporated into the melt, introducing hydroxyl group into the finished glass. These hydroxyl groups act as deterrants to the polymerization reaction and the resulting glass is strongly attacked by boiling water. H_3PO_4 forms a high-boiling eutectic with H_2O (B.P. = 866° C.) and it is difficult, if not impossible, to eliminate the hydroxyl groups from the melt if said eutectic is present. The only alternative appears to be to remove the excess H_3PO_4 from the salt precursor prior to the heating procedure.

The problem resolves itself into the fact that both the monomer and the excess H_3PO_4 are water soluble. I have found that certain non-aqueous solvents will preferentially dissolve the H_3PO_4 leaving a crystalline salt. Such solvents include the following: acetone, methyl ethyl ketone, methyl acetate, ethyl acetate, n-butanol. In general, the ketones, acetates, and higher molecular-weight alcohols are suitable for H_3PO_4 dissolution. However, I have determined that for most divalent salt precursors, acetone remains the best washing agent. The excess H_3PO_4 is completely removed by appropriate steps in the washing procedure. Acetone is appropriate for Ca, Sr and Ba salt precursors, whereas methyl ethyl ketone is preferred for Al, Be, Mg, Zn and Cd salt precursors as a washing agent to completely remove excess H_3PO_4. I have also determined that excess H_3PO_4 is critical for the metaphosphate glass compositions of Ca, Sr, Ba, Cd and Zn, whereas it is not essential for Be, Mg or Al. When the monobasic salt precursor

reacts, it loses its waters of hydration, forming an anhydrous salt. This precursor salt then reacts to form either of several intermediates. I have found that when H_3PO_4 is completely absent, $Ca(H_2PO_4)_2$ reacts to form $Ca_2H_2P_4O_{13}$, a tetrameric ring product containing hydroxyl groups. This then further reacts to form a melt containing hydroxyl groups, substantially having the formula:

$$CaP_2O_{\frac{12-x}{2}}(OH)_x$$

wherein x has a value of at least 2.

As the melt is held at a temperature of the order of about 1050° C., the constituent hydroxyl groups condense to form water and the polymerization reaction proceeds still further. When the hydroxyl groups have been eliminated, the polymerization is complete and a high durability $[Ca(PO_3)_2]_n$ glass results, where n denotes a degree of polymerization of at least about 4. If excess H_3PO_4 is present, then the $Ca(H_2PO_4)_2$ monomer reacts in a different manner, to form the initial acid pyrophosphate, to form a melt having a formula;

$$CaP_2O_{\frac{12-y}{2}}(OH)_y$$

where y is greater than x as given in the first formula and depends on the amount of excess of H_3PO_4 present. The resulting glass is much less stable as shown by the data in Table I which also shows the chemical durability of $[Mg(PO_3)_2]_n$ and $[Al(PO_3)_2]_n$ and $[Al(PO_3)_3]_n$ glasses and their lack of criticality to the presence or absence of excess H_3PO_4.

TABLE I

$Ca(PO_3)_2$ Glass	Excess H_3PO_4	Chemical Durability (Loss in mg/cm²/hr)
(a) Prior Art	not known	~2.2 to 24.0
(b) Stoichiometric	~.05%	0.22
(c) Stoichiometric	+5%	0.53
(d) Unwashed Crystals	−25%	0.63
(e) Stoichiometric	+100%	2.20
$[Mg(PO_3)_2]_n$ Glass	none	0.085
$[Mg(PO_3)_2]_n$ Glass	+100%	0.135
$[Al(PO_3)_3]_n$ Glass	none	0.000054
$[Al(PO_3)_3]_n$ Glass	+100%	0.0071

This relative instability may be explained as follows. A melt of $Mg(PO_3)_2$ glass is not obtained until the temperature of 1100°–1150° C. is reached. A melt for $Al(PO_3)_3$ is not attained until 1300°–1350° C. At these temperatures, any excess H_3PO_4, in the form of the high-boiling (866° C.) eutectic has long since disappeared. Because a melt is obtained at 950°–960° C. for $[Ca(PO_3)_2]_n$ glass, the excess H_3PO_4 *can* be incorporated into the glass. Thus, the chemical durability of $[Ca(PO_3)_2]_n$ glasses are very dependent upon the amount of H_3PO_4 present prior to melting to form the glass, as shown above. When a calcium monobasic salt, analyzed by thermogravimetric analysis to contain about 0.05% H_3PO_4 by weight, was reacted in an alumina crucible to form a melt and held for 96 hours to effect complete polymerization, the resulting annealed glass showed a chemical durability (hydrolysis loss) of 0.22 mg/cm²/hr. The same salt, in the presence of deliberately added H_3PO_4, produced glasses whose hydrolysis loss increased as the initial H_3PO_4 increased. Essentially, the same mechanism applies when the cation is Sr, Ba, Cd and Zn.

I have determined that the initial melt of $[Ca(PO_3)_2]_m$ glass transforms slowly over a period of time into another form of the glass:

$$[\beta\text{-}Ca(PO_3)_2]_m \xrightarrow[1050^\circ C.]{110 \text{ hours}} [\alpha\text{-}Ca(PO_3)_2]_n$$

where m and n denote a degree of polymerization and $m << n$. For full polymerization, about 110 hours at 1050° C. are required for the $Ca(PO_3)_2$ melt whereas 120 hours are required for the $Ba(PO_3)_2$ melt. β and α denote different forms of the polymeric glass. Excess cation may be added to the melt in the form of MCO_3, $M(OH)_2$ or $MHPO_4$ and $M_2P_2O_7$. The resulting glass is less stable to hydrolysis etching by boiling water by as much as factors of 10. For example, an exactly stoichiometric $Ca(PO_3)_2$ glass has a hydrolysis loss of 0.11 mg/cm²/hr, whereas a glass containing 15 mol% excess calcium, $[\alpha\text{-}Ca_{1.15}(PO_3)_2]_m$, has a hydrolysis loss of 0.86 mg/cm²/hr. Thus, I have established that it is the exact stoichiometric metaphosphate formulation which exhibits maximum resistance to hydrolysis etching in boiling water, in contrast to resistance of glasses of the prior art.

Chemical durability appears to be affected also by the crucible material which may contribute impurities from dissolutions of the crucible. For example, in starting with a $Ca(H_2PO_4)_2.H_2O$ precursor salt which contains about 50 ppm of impurities, including Fe, Sr, Na, Co, Si, Cr, Mn, K and Li, a glass is made by melting the precursor in a high-purity alumina crucible. Part of the crucible wall is dissolved by the melt and the obtained glass is found to contain about 2200 ppm of impurities of which 1800 ppm is Al_2O_3. It is this glass which exhibits a hydrolysis loss of 0.24 mg/cm²/hr. The loss occurs at the places where the 2200 ppm of impurities are isolated and concentrated. The bulk of the glass does not seem to be affected by the boiling water. Crucibles composed of silica zircon ($ZrSiO_4$), gold, and carbon must be avoided completely since these crucible compositions react with the melt and the resulting glass is massively degraded by boiling water. The transition metals are also reactive resulting in a glass which is very vigorously attacked by boiling water. Crucible materials found most suitable are alumina (Al_2O_3) and platinum. Although both of these also react with the melt, the reaction is slow enough that these crucible materials are usable. In order to cause the initial polymerization of the salt precursor to proceed, I have found that it is desirable to program the heating from the beginning through a series of stages of sequentially increased temperatures (i.e. in a controlled heating cycle without intermediate temperature decrease) through the melt stage. For the calcium metaphosphate glass precursor, the temperature is programmed at a rate of about 6° per minute to 175° C. where the hydrate water is lost. The temperature is held for 30 minutes and then raised by programming at an increase of 6° C. per minute to 290° C., where it again is held for 30 minutes. The temperature is then programmed to 410° C. where it is held for 30 minutes and then is programmed to 980° C. at a rate of 6° C. per minute where the melt is obtained. Thereafter a final melt temperature of 1050° C. is attained and the melt is held for the prescribed time of about 110 hours. This procedure results in a glass with increased chemical durability over the glass which is obtained through non-programming procedures. The tempera-

tures cited above are specified only for the calcium mono-basic phosphate system. Each cation has its own characteristic reaction temperatures which are similarly determined. I have further discovered that if the heating cycle to initiate polymerization to form the melt is interrupted, and the material is cooled and then reheated to form the melt, the resulting glass is less stable to hydrolysis etching than that glass obtained from a continuous heating schedule. For some applications the product obtained of this stage may be advantageous. The rate of initial heating does not seem to critical and the precursor can be caused to form a melt in as little as one-half an hour or as long as 6 hours without causing an observable change in resistance to hydrolysis etching by boiling water.

The invention will be further described by the following specific examples. It will be understood, however, that although the examples detail certain specific compositions and conditions of the invention, they are provided primarily for purposes of illustration and the invention in its broader aspects is not limited thereto. Unless expressly stated otherwise, parts expressed are parts by weight.

EXAMPLES I-III — Calcium Phosphate Glass

(I)

(a) Prepare a solution of H_3PO_4 in water by adding approximately 3.00 mols H_3PO_4 (210 ml) to 600 ml H_2O and dilute to 1000 ml total volume; 85% H_3PO_4 — reagent grade is used.

(b) Weigh out 100.1 gm $CaCO_3$ and slowly dissolve in H_3PO_4 solution.

(c) Weigh out 2.5 gm of ammonium 1-pyrrolidinedithio-carbamate (APC) and dissolve in 50 ml of water. Add this solution to the phosphate solution. A dark grey precipitate forms.

(d) Filter the solution through a 0.45 micron filter to remove the precipitate.

(e) The purified solution is evaporated slowly, using a steam bath, if desired, to obtain crystals plus a liquor. The liquor is H_3PO_4 plus a small amount of H_2O. The excess liquor is decanted and the crystals are washed in acetone, or other suitable solvent by a suspension and decantation procedure to remove all of the excess acid. Even a very small amount of H_3PO_4 left in the crystals tends to produce a glass which is not stable to hydrolysis and the excess H_3PO_4 must be removed. The resulting crystals have a total impurity content of 100–200 ppm.

(II)

Alternately, if a crystalline salt of higher purity is desired, the following purification procedure is used. Step (a) is followed by step (c) and the resulting solution is filtered as in step (d). Then the $CaCO_3$ is added as in step (b) and steps (c) and (d), are again performed prior to the evaporation step (e). The resulting crystals have a total impurity content of about 100 ppm.

(III)

If an even higher degree of purity is desired, then the procedure of (II) is again followed and the resulting solution is placed in an electrolysis unit equipped with a stirred mercury pool cathode, a gas diffuser for introduction of nitrogen bubbles into the solution, and a platinum anode. The nitrogen gas is turned on and the solution is electrolyzed at −2.75 volts direct current at the mercury pool for a time sufficient to remove ionic metallic impurities. Step (e) is then followed. The resulting crystals have a total impurity content of about 50 ppm.

(f) The crystals of the monobasic salt of (I), (II) and (III) are placed in a clean alumina crucible of suitable size and heated to 1000° C. to cause chemical condensation and polymerization to proceed. The salt decomposes, condenses, and polymerizes to form a clear glassy melt. The melt is held in air for at least 96–110 hours to complete polymerization. The clear glass melt is then cast in desired shapes and processed to relieve internal stress by annealing.

(g) Alternately, the crystals are placed in an alumina crucible and the temperature is programmed through temperature steps corresponding to chemical reactions and condensations as determined by differential thermal analysis. The reaction products are then melted by increasing the temperature to 1050° C. and then processed according to step (f) to cause complete reaction. The programming procedure prior to melting markedly increases the durability of the obtained glass.

EXAMPLE IV–Strontium Phosphate Glass

(a) The general steps of Examples I-III are followed except that in the case of strontium phosphate glass, 147.63 gm $SrCO_3$ are substituted for the $CaCO_3$ in step (b) of the prior examples.

(b) Following the evaporation procedure of step (e) in Examples I-III the excess liquor is poured out and the crystals are washed in acetone by suspension and decantation until the excess phosphoric acid is removed.

(c) Depending upon degree of purity desired, any of the purification procedures of Examples I-III can be used.

(d) The general procedures of steps (f) and (g) of the prior examples are then followed to prepare a strontium phosphate glass of high chemical durability, as compared to those glasses of the prior art.

EXAMPLE V — Barium Phosphate Glass

(a) The general procedures of Example IV are followed except that 197.35 gm $BaCO_3$ are substituted for the $SrCO_3$ of step (b) of that example.

(b) Following the evaporation step, the crystals are washed in acetone to remove excess phosphoric acid.

(c) The crystals are then melted according to the procedures of the prior examples to form a substantially homogeneous melt which is allowed to undergo condensation and/or polymerization until reaction is complete.

(d) For the barium phosphate salt, the temperatures of reaction are lower than those of calcium phosphate salt and the melt is obtained at a lower temperature of about 925° C. Care must be exercised not to allow the melt temperature to rise over about 1200° C., since phosphorous in the melt is lost as volatile P_2O_5, thereby degrading the quality of the so-obtained glass.

EXAMPLE VI — Magnesium Phosphate Glass

(a) The general procedures of Examples I-III are followed except that in step (b), 84.32 gm of $MgCO_3$ are substituted for the $CaCO_3$.

(b) In following the evaporation procedure (e) of Examples I-III, it is found that crystals of magnesium monobasic phosphate trihydrate do not form easily. Therefore, the procedure is modified as follows: The

solution obtained from step (d) (Examples I–III) is evaporated on a steam bath until about 80% of the volume is lost. The remaining 20% of the solution is then cooled and placed in a separate container to crystallize. After about 48 hours, the liquid condenses into a solid mass of crystals.

(c) Because the magnesium phosphate salt does not form a homogeneous melt below about 1100° C., it is not necessary to remove excess H_3PO_4. During the evaporation process, the excess phosphoric acid forms an eutectic compound of $7H_3PO_4.3H_2O$ which boils at about 866° C.

For the case of calcium phosphate glass which melts at about 935° C., a substantial amount of the eutectic compound remains at the 935° C. melting point and is incorporated into the glassy melt.

For the case of the magnesium phosphate glass, all of the eutectic can be boiled off before the glass melt obtains. Therefore, it is not necessary to remove the excess H_3PO_4 prior to the condensation and melting procedure to obtain a substantially homogeneous melt. Therefore, the crystals plus liquid are placed on a filter and the liquid is removed by suction to a degree of practical necessity as desired.

(d) The wet salt is placed in a crucible and the temperature is raised slowly to about 950° C. whereupon the eutectic compound vaporizes and is lost. The temperature is held at 950° C. until of all of the excess acid-water eutectic is substantially lost from the crucible containing the magnesium phosphate salt, whereupon the temperature is raised to about 1100° C. to obtain a homogeneous melt. This melt is then processed further as given in Examples I–III.

(e) If it is desired to obtain crystals free from excess H_3PO_4 the magnesium phosphate salt can be washed by suspension and decantation in methyl ethyl ketone. The salt is then processed as before.

EXAMPLE VII — Beryllium Phosphate Glass

(a) The procedures of Example VI are followed except that 56.03 gram $BeCO_3.Be(OH)_2$ are substituted for the $MgCO_3$.

(b) Since beryllium is known to be a toxic element, proper precautions regarding prevention of ingestion by humans are maintained. Once the beryllium is in the form of phosphate glass, its toxicity is considerably lowered as compared to solution and melt forms encountered during processing to form the glass.

EXAMPLE VIII — Aluminum Phosphate Glass

(a) Prepare a H_3PO_4 solution by adding 485 ml of 85% H_3PO_4 (reagent grade) to 500 ml H_2O. Dilute to 1000 ml total volume. This solution may be purified according to methods given in Examples I–III.

(b) Weigh out 78.00 gm $Al(OH)_3$ and dissolve in H_3PO_4 solution.

(c) Purify resulting solution by techniques of Examples I–III.

(d) Evaporate to obtain crystals of aluminum monobasic phosphate, according to techniques of Examples I–III.

(e) Since the glassy melt is not obtained much below 1350° C., it is necessary to remove the excess liquid acid by washing techniques. The prefiring schedule of Example VI(d) is preferred except that the final temperature to obtain a melt is 1350° C. instead of 1100° C.

(f) The substantially homogeneous melt is held at 1350° C. for a time required to effect complete intrareaction and polymerization of the melt. The melt is then cast and annealed to form an aluminum phosphate glass with markedly improved properties over that of the prior art.

EXAMPLE IX — Zinc and Cadmium Phosphate Glasses

(a) The general technique of Examples I–III are used with the following exceptions:

(b) Select the desired phosphate and substitute one of the following for the $CaCO_3$ of Example I:

81.37 gm	ZnO
172.41 gm	$CdCO_3$

Dissolve in the H_3PO_4 solution to form a completely homogeneous solution.

(c) In the case of zinc or cadmium solutions, the use of cupferron is recommended as an organic precipitant in place of APC since the latter forms insoluble precipitates with these two ions. Cupferron only partially precipitates these ions and can be used successfully to purify either of these solutions.

(d) Following solution purification, the salts of Cd or Zn are prepared in the manner of Examples I–III.

(e) The crystals of Cd or Zn monobasic phosphates cannot be washed in acetone since they are soluble therein, but methyl ethyl ketone can be used successfully to remove the excess acid to obtain a purified salt, as described in Examples I–III.

(f) The glasses are prepared as given in Examples I–III, except that the temperatures critical for Cd, or Zn, monobasic salts, as predetermined by differential thermal analysis, are employed.

Although I have described but a limited number of products and methods for preparation according to the present invention, it will be apparent to those skilled in the art that variations in both compositions and methods may be effected within the spirit of the invention. Accordingly, the invention is not to be limited except as required as requied by the appended claims.

I claim:

1. A method of preparing a polymeric phosphate glass having the formula:

$$[M(PO_3)_b]_n$$

where M is a single metal ion, to the exclusion of other metal ions, selected from the group consisting of aluminum, zinc, cadmium and the alkaline earth metals, beryllium, magnesium, calcium, strontium and barium, where "*b*" is 3 for aluminum and 2 for the other metal ions, and "*n*" is a degree of polymerization of at least 4, which comprises forming a solution of said metal ion M and phosphoric acid by dissolving a compound supplying said metal ion M in a controlled excess of phosphoric acid to form a stoichiometrically proportioned solution, adding a precipitating agent effective to precipitate soluble transition metal impurities other than the selected metal ion, removing formed insolubles to produce an essentially pure solution, forming a crystal product from the resulting purified solution by evaporation, washing said crystal product substantially free of phosphoric acid to yield a stoichiometrically proportioned crystalline phosphate salt, heating said crystalline salt in a controlled heating cycle in the substantial absence of phosphoric acid or other phosphate or metal

ion compounds until a polymerized melt stage is attained, and continuing the polymerization until polymerization is substantially complete and a homogeneous glass is formed.

2. The method of claim 1 wherein M is calcium.
3. The method of claim 1 wherein M is strontium.
4. The method of claim 1 wherein M is barium.
5. The method of claim 1 wherein M is magnesium.
6. The method of claim 1 wherein M is beryllium.
7. The method of claim 1 wherein M is aluminum.
8. The method of claim 1 wherein M is zinc.
9. The method of claim 1 wherein M is cadmium.
10. The method of claim 1 wherein the ratio of metal ion to phosphate group in the homogeneous glass from the melt is about 1:2.
11. The method of claim 1 wherein the heating is intercoupled at the stage where an initial polymerization product has formed and then cooling the compound prior to producing said melt.
12. The method of claim 1 in which the controlled heating cycle comprises a sequence of progressively increasing heating cycles to the melt polymerization stage.

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